General Policy Issues

Consumer reporting of adverse drug reactions

Effective use of medicines depends on the availability of reliable information. Where adverse reactions and interactions of drugs are concerned, existing systems of adverse drug reaction monitoring by health professionals are an important tool for collecting, collating and analysing data as a means of establishing new knowledge and generating early signals of possible drug complications not reported through clinical trials. Output from such adverse drug reporting systems complements the information appearing in the published literature and from other studies. However, for a number of reasons these systems have important deficiencies and limitations and they cannot stand alone. Adequate feedback is needed from users of medicines.

The following is an extract from a consensus document developed during the First International Conference on Consumer Reports on Medicines (CRM) held from 29 September to 1 October 2000 in Sigtuna, Sweden. The meeting was attended by participants from the medical and pharmaceutical professions, drug regulatory authorities, consumer associations and the World Health Organization.

There are both general and specific reasons to support the development of consumer reporting as an essential component of drug safety. It is also an important mechanism for consumer empowerment in health, which extends to processes such as regulation and clinical trials. Consumer reporting promotes:

1. Consumer rights and equity, including fairness since it is the patient who assumes the risks and the costs; the fundamental right to express oneself, to be listened to; and the right to informed consent.

2. Consumers have unique perspectives and experiences. They can provide information and insight which is crucial to advancing the effective and safe use of medicines. The sharing of information in a public reporting system also encourages consumers to help one another.

3. The medical establishment can profit from the discipline of consumer input since the standard of practice can only benefit from an ongoing and active encounter with consumer concerns. Consumers for their part need a willing ear and a channel through which to make their experiences and feelings known as they assume the risks and costs of using medicines. They are also exposed to the relationship between benefits, harm, and costs of drug use, and can themselves contribute to knowledge of that relationship.

Limitations of physician-based and pharmacist-based reporting

Adverse reaction reporting systems have evolved considerably since their creation and play a significant role in mobilizing data. However, they have certain serious limitations. Foremost among these is the fact that only a small proportion of practising physicians (often less than 5%) and a relatively small number of pharmacists (varying from country to country) contribute data. Consequently, information on suspected adverse reactions communicated by a patient to his physician stands a 95% chance of going no further and making no contribution to adverse reaction reporting.

There are various well-documented reasons why a health professional may fail to report to the system an adverse effect communicated to them by the patient. The effect may be sufficiently well-known already, or conversely it may be dismisses as being unlikely, vague or unrelated to the treatment. However it also seems clear that the prescriber may perceive risk and adverse events differently from the patient. While, for instance, the doctor is likely to accept the existence of any tangible or visible physical reaction (e.g. a rash), he or she is less
likely to appreciate that a consumer’s description of experiencing ill-defined malaise, unease or changes in mental state may equally constitute an early sign of drug complications. Some physicians appear particularly hesitant to report adverse reactions to a drug which they have prescribed for a non-approved indication (“off-label use”). In some countries, physicians have been more generally reluctant to submit adverse reaction reports to official systems because of a fear that, particularly where a reaction is serious, the prescriber may be blamed and accused of malpractice.

Above all, however, the physician who has no interest in communicating suspected adverse reactions to a central system will take no action. What may be significant information then remains buried in the patient records. It should be added that there is also a problem relating to under-reporting by patients to physicians, especially where a patient is nervous about raising the issue. This situation is regrettable, but it exists, and some consumers in this situation would be less reluctant to report their experiences to a neutral consumer-based system. The prescriber could and should do more than is usually done to alert a patient to the need to report suspected adverse reactions, whatever reporting channel is used. This is particularly important where a new drug is prescribed, or an old drug is administered for a new or unusual indication.

A final problem with existing systems is that the input relates primarily to new drugs; reports of adverse experiences with products which have been marketed for many years are relatively few, despite the fact that new problems can emerge with such drugs even after decades of use and that old drugs may be redeveloped for new indications (e.g. thalidomide for treatment of acute lepromatous reaction). The establishment of direct consumer-based reporting of suspected unwanted events can compensate for these and other deficiencies in existing systems.

Benefits and challenges of consumer reporting

Some positive and direct benefits of direct consumer reporting can be identified.

1. There is evidence from the field that direct consumer reporting can result in an earlier accumulation of signals, some of which will point validly to new and hitherto overlooked reactions. In at least one comparative study, consumer reports have been found to cover a wider spectrum of organ systems and adverse reactions than reports entering a physician-based system.

2. Direct reporting can provide exceptionally informative, vivid and more complete accounts of unwanted experiences which do not readily lend themselves to classification in any rigid system. These may include mental reactions but also adverse changes in the quality of life which can be very important, real and distressing to the medicine user yet are unlikely to be clear to a prescriber.

3. Because consumer reporting can cover situations about which the physician is not informed and about which he or she therefore cannot report, it is bound to provide information which is not normally available to existing systems. Where, for example, a patient discontinues a drug because of an adverse effect, and does not return to the prescriber, the latter will have no knowledge of the event. Again, if patients experience a suspected reaction to a self-medicated drug, or to a traditional, herbal or alternative medicine which they have taken at their own initiative, no prescriber is likely to know about it. It is clear that in much of the world there is extensive self-treatment involving drugs which formally are restricted to prescription sale, and these include new and potent products with still poorly defined risks.

Similarly, if a patient is being treated by two physicians (e.g. a general practitioner and a specialist) the one may not be aware of drugs prescribed by the other, and adverse reactions or interactions will be missed. The onus of ensuring proper collaboration and communication in this matter clearly lies with physicians and the health system, but where it fails, a consumer-based system may well provide important input.

Present barriers to consumer participation

In addition to the above challenges, a series of reasons can be advanced as to why consumer experience so far has not been mobilized as a tool to develop new knowledge and monitor possible adverse reactions. The most obvious of these is the fact that in most countries, reports submitted directly by patients or their representatives are not accepted by the existing physician-based systems. They may be formally excluded, or those managing the systems may simply be reluctant to accept them.
In addition, however, consumers have not yet played an active role. Reasons for this include lack of knowledge regarding drugs and their reactions, a difficulty which is universal but especially severe in countries where lack of education and illiteracy are widespread. In some countries medical mysticism is still dominant; characterized by a desire to maintain secrecy around medical facts and thinking. Improved public education and information services, coupled with more modern attitudes on the part of professionals, can do much to remedy this.

The fact that drugs are often prescribed and used irrationally creates other difficulties, for example where many drugs are given for a single condition when only a single drug is indicated. In much of the world, the patient has only a brief interview with the physician before receiving a prescription or therapeutic advice, and there is neither an opportunity nor a positive tradition favouring information and advice about the drug that has been prescribed or recommended.

A particular problem in some developing countries is that a patient may not know with which drug he/she has been treated or which dose he/she has received. Not only are drugs sold under a multitude of names, but in some instances they are referred to anonymously (“take two of the blue tablets and three of the green ones every day”) or dispensed without labelling (in sachets containing a few loose tablets, for example). In such situations, the active participation of users will be difficult to achieve for many years to come.

In industrialized countries, medicine users increasingly report their experiences on internet-discussion sites, or to patient and consumer organizations. These reports however tend to be left as anecdotal experiences. They are not taken seriously as consumer reporting. Even in countries where the above barriers are severe, a start can be made by mobilizing consumers in the more educated classes to take part in a limited venture which will subsequently extend into a wider movement.

A structure for consumer reporting
No single structure is likely to prove ideal for all countries. However, a number of firm impressions as to preferred structures can be recorded.

Responsible body
The scheme should be handled by an independent body at arm’s length from government and industry as far as data gathering and interpretation of information are concerned. The body should be able to call upon independent experts, including pharmacists, pharmacologists and physicians with experience in assessing cause-effect relationships, but it should also have expertise in consumer affairs and patients’ rights.

Reporting channels
Reports should be submitted through the most appropriate route, depending on the current situation in the country; the submission procedure should be as simple as possible. In some parts of the world the Internet provides a widely available means of reporting, whereas in others the mail, telephone or personal contact are more appropriate.

Form of reports
Existing physician-based systems have shown that it is helpful to receive the essence of a report in a standardized manner. Well-designed reporting forms should ideally be used. Reports received by telephone, letter or through personal contact should be transferred to such forms, but with retention of a complete description of the event which has been provided, e.g. by scanning a letter or recording the description given by telephone. The data as recorded on the standard form should be sufficiently exact to permit digital analysis, while a plain text description of the complication should also be provided since it can be valuable in recognizing unusual events not readily amenable to coding. As in professional reporting systems, great care must be taken to ensure anonymity so that personal medical data do not become common knowledge.

Terminology
As became clear at an early stage with professional reporting systems, there will be a need to standardize terminology, particularly bearing in mind the fact that information will arrive from different cultures and in different languages. It is possible that in this respect the system will be able to benefit from the work carried out by the Uppsala Monitoring Centre.

Examination
Every adverse reaction report received should be examined and considered. As with existing physician-based systems, it will be important to have adequate information about the user, the treatment details, timing and course of the reaction itself. A causality analysis should then be attempted, recognizing that there is no exact methodology to this end. An attempt should be made to determine whether the report is novel or whether it has previously been described in existing systems or in the
literature. The methods of analysis will not differ greatly from those developed in the best existing professional-based systems, but a consumer perspective ("how was this event experienced by the user?") should be included.

**Direct feedback**
Experience with existing adverse drug reaction reporting systems shows the great importance of acknowledging promptly the receipt of every report, and following this up in due course with a full reply and, where possible, an explanation and reassurance.

**Information to others**
The individual report is essentially confidential and under no circumstances should the name of the reporter, or any data on the basis of which the reporter might be identified, be transmitted to other parties. However, general information on the nature of reports received on a particular drug should be made available, together with the relevant assessment, to all interested parties. These are likely to include the national professional-based adverse reaction reporting scheme, the official drug regulatory authorities, the health professions, agencies responsible for rational drug use policies and programmes, the manufacturer, consumer and patient organizations and others likely to need the data. The media should have full access to the analysed data.

When providing information, disclaimers similar to those employed by existing spontaneous reporting systems should be added, so as to reduce any risk of over-interpretation or unnecessary alarm. In many instances periodic reporting on data input (e.g. quarterly) will be adequate, but it will be appropriate to disseminate groups of related reports that suggest the emergence of a hitherto unrecognized problem more urgently.

**Collaboration**
At the very least, there should be an exchange of data between public reporting schemes in different countries to strengthen systems and a further acceleration in the identification of new data. There is strong interest in establishing a global centre for consumer reports, analogous to that existing for professional reporting to The Uppsala Monitoring Centre but separate from the latter. The Uppsala Centre is, however, open for an input of data from the consumer system, which could form a separate database. The Centre currently holds the data from 59 national physician-based schemes and provides reports and analyses of this worldwide material, as well as conducting methodological research. Its experience and advice could be of great value in developing consumer systems.

**Action required**
A careful distinction must be made between a neutral system for collecting, analysing and disseminating data and an institution taking positive action in the light of emergent findings. While, as noted above, the system can and should bring its findings to the attention of other parties and agencies, it is likely to gain greatest respect if it concentrates single-mindedly on the most balanced possible analysis of data and the generation of signals. It would be more appropriate for bodies primarily concerned with the active promotion of patient and consumer interests to take whatever action seems justified in the light of such findings.

**Hospital reports**
Appropriate arrangements may be made to enable hospitalized patients to report directly to the proposed scheme when they experience the need to do so, either during their hospital stay or later.

**Reports from trials**
It would be very desirable for patients and volunteers taking part in clinical drug trials to report adverse reactions when they so wish to a central system. It is well known that many adverse reactions occurring in trials provide early pointers to drug injury, and that the data in question sometimes fail to become generally known either in a timely manner or at all. In particular, adverse reactions experienced by subjects dropping out of a trial may be lost to the records despite the fact that these events may provide the first indications of a serious problem. The principle of the subject's freedom to report should be laid down in guidelines such as those for Good Clinical Practice.

The same principles should be incorporated in clinical trial protocols subject to approval by ethics committees and analogous bodies. Confidentiality agreements concluded between an industrial sponsor and a clinical investigator should never be allowed to impede reporting of adverse reactions by participants.

**Active reporting**
Over the years, there have been several successful ventures into "intensive monitoring" or "active reporting", seeking to obtain integral registration of all adverse events from a particular pa-
tient group or at a particular location. Such efforts are justified, where there is a special reason to anticipate certain problems and to quantify them within a short period.

**System monitoring**
The functioning of all aspects of a system of this type should be monitored internally and its usefulness should be evaluated periodically so that modifications can be introduced as necessary. Field trials of modified procedures may be called for.

**Secondary services**
It seems clear from experience that once consumers have established contact with the proposed system they will seek supplementary services from it, in particular requesting advice and information. While the system should refer requests for medical advice to the most appropriate body (generally the patient’s own physician) sympathetic assistance should be given where factual information or reassurance is sought. Such information may also need to be communicated to other bodies, especially where it points to a problem which, though it may not concern adverse reactions, demands attention and correction. Finally, much information regarding adverse drug reactions is now to be found on the Internet, although it is scattered and of variable reliability. Consumer reporting systems could in due course perform a useful role by periodically sampling the relevant content of the Internet and disseminating selected data that appear significant.

**Pitfalls and problems**
Past reasons for rejecting the principle of direct consumer reporting need to be borne in mind since they can provide pointers to necessary action. The opinion that information emanating directly from consumers is less reliable than that communicated by way of physicians (or pharmacists) is only valid insofar as the professional reporter may provide preliminary screening and useful background information when submitting the report. Provided there is proper feedback and careful expert analysis of reports, it will not necessarily be more difficult to eliminate mischievous, misleading or ambiguous reports than has been the case in professional-based systems, where entirely similar problems arise. A problem deserving particular attention, especially in international collaboration between systems, is that of translation and interpretation. Concepts regarding drug safety and subjective experiences (e.g. concerning the quality of life) may prove difficult to translate from one language to another, and plain text accounts of experiences may simply be difficult to comprehend when read in a different environment. These are intercultural as well as linguistic challenges.
Vaccines and Biomedicines

Quality assurance and safety of biologicals

Because of their unique origin, biological products derived from normal or genetically-modified living organisms offer particular challenges concerning requirements for quality, safety and efficacy. Biological products are used in the diagnosis, treatment or prevention of disease, and include vaccines, blood, blood products, hormones, cytokines and a range of cellular technologies. To ensure the quality, safety and efficacy of these products, regulatory guidance, the provision of standards, and the design of appropriate tests must be provided which are in line with latest developments.

WHO, through its Expert Committee on Biological Standardization (ECBS), plays a key role in reviewing scientific progress and in establishing International Reference Preparations and Recommendations on production and control of biological products. The report of its Fifty-first meeting, held in November 2000, is summarized below.

Oral polio vaccine

WHO Recommendations (formerly requirements) for Oral Polio Vaccine (OPV) were revised at the Fiftieth meeting of the ECBS in 1999, and new quality control procedures introduced. These included the use of transgenic mice as an alternative to the neurovirulence test in primates for type 3 oral polio vaccine, as well as a test for the molecular consistency of production of the live virus vaccine (MAPREC assay).

At the Fifty-first ECBS meeting, data concerning the use of the transgenic mice model for testing the neurovirulence of types 1 and 2 were reviewed. The ECBS concluded that the mouse model provided an alternative neurovirulence assay also for types 1 and 2 oral polio vaccines and agreed to include this recommendation as an addendum to the updated Recommendations for Oral Polio Vaccine. However, it would be necessary for laboratories intending to use the alternative assay to follow standard training and implementation procedures. A programme of training and staged implementation has therefore been developed by WHO, with the collaboration of the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, USA, and the National Institute for Biological Standards and Control (NIBSC), United Kingdom, in order to facilitate the introduction of the new assays.

Inactivated polio vaccine

Updated Recommendations for Inactivated Polio Vaccine (IPV) were also adopted by the ECBS. The Recommendations (formerly requirements) for Inactivated Polio Vaccine were last revised in 1985 and there have been several advances in vaccine production technology and quality control since that time. Furthermore, as the goal of eradicating poliomyelitis due to wild-type polio viruses is in sight, laboratories that use wild polio viruses will become an important potential source of accidental reintroduction of wild virus into the community. To minimize this risk, WHO has developed a global action plan that requires increased biosafety containment of wild polio viruses (1). This applies to parts of the production process for IPV where wild polio viruses are used. For these reasons, it was essential for the IPV Recommendations to be urgently updated. The ECBS reviewed a draft which had already undergone considerable international consultation and, after making some comments, adopted the draft as the new Recommendations for Inactivated Polio Vaccine.

Production and control of Japanese encephalitis vaccine

Japanese encephalitis is a major cause of viral encephalitis in the Asia-Pacific region. A live-attenuated vaccine has been developed in China...
where it has also been licensed and used for a number of years as an alternative to existing inactivated vaccines. Several countries are interested in using the live attenuated vaccine.

Guidelines for the Production and Control of Japanese Encephalitis (JE) Vaccine (live) for Human Use were adopted by the ECBS. The document provides information and guidance concerning the history, characteristics, production and control of live attenuated Japanese encephalitis vaccine and is designed to facilitate progress towards the eventual international licensing of the vaccine. The text is written in the form of guidelines rather than recommendations since further work is needed to develop and standardize appropriate methods and criteria for certain tests, such as the neurovirulence test.

Diphtheria, tetanus, pertussis and combined vaccines

A WHO Working Group recommended the development of a simple, robust and standardized assay to demonstrate consistency of immunological characteristics suitable for lot release of vaccines containing diphtheria and/or tetanus toxoid. The ECBS therefore discussed a proposal to amend the present requirements for diphtheria, tetanus, pertussis and combined vaccines to permit the use of a test procedure based on serological assay for this purpose. The ECBS endorsed the need to work towards a common model acceptable by all parties, provided that new problems were not created. The ECBS welcomed the steps already taken, but concluded that further work was necessary before any changes could be made to the present Recommendations. Further work on this issue is in progress.

A range of single component and combined acellular pertussis vaccines are now available. However, ethical considerations prevent clinical protection studies of new vaccines or vaccine combinations and so the need exists for a suitable animal model to evaluate vaccine potency. The immunogenicity of these vaccines does not necessarily reflect clinical efficacy. Studies of appropriate animal models to assess the protective activity of acellular pertussis vaccines are under way, and a respiratory challenge model appears to offer a good prospect for product characterization. Further studies of this model are planned as well as studies to assess the value of the modified intracerebral challenge assay of acellular pertussis vaccine as a discriminatory lot release assay.

Transmissible spongiform encephalopathies

The ECBS attaches considerable importance to measures undertaken to ensure the safety of vaccines and blood products with respect to transmissible spongiform encephalopathies (TSEs).

At its Fifty-first meeting, the ECBS discussed the current situation regarding measures taken to exclude materials possibly carrying bovine spongiform encephalopathy (BSE) from the production of vaccines and other biologicals, including issues related to the use of bovine serum and other bovine derived materials. Recent risk assessments, carried out in the USA and European Union, agree that any risk from vaccines and other biologicals is theoretical and negligible.

The safety of vaccines and other biologicals with respect to BSE is considered to be assured by a combination of sourcing of materials used in manufacture from safe sources with respect to country/ herd/ animal and by employing only tissues with no demonstrable infectivity. Furthermore, in relation to the safety of vaccines and other biologicals prepared from mammalian cells there is no evidence that the transmissible agent of BSE is capable of amplification in cultures of the non-neuronal cells that are currently used as substrates for production. Nevertheless, in view of rapid developments in this area the ECBS recommended that WHO should review the situation and update its report on Medical and Other Products in relation to Human and Animal Transmissible Spongiform Encephalopathies (2).

In addition, the ECBS noted that progress is being made by the Working Group on International Reference Materials for Diagnosis and Study of TSEs in the development and evaluation of essential human-derived reference materials. Efforts of the Working Group are aimed at the standardization of diagnostic procedures under development. The need for international reference reagents and panels to compare new diagnostic procedures for TSEs was considered to be a priority. Reports of these developments are published on the WHO Website at the following address: http://www.who.int/technology/biological.html.

International standards

The ECBS established 6 new or replacement International Standards and Reference Reagents covering a range of products (Table 1, page 220).
Additionally, one International Reference Material is no longer needed and was discontinued following a public consultative process (3). Table 2, page 220). Also, due to a decrease in use or following a change in international requirements, the ECBS proposed to discontinue a number of reference materials at its next meeting subject to public comment to this notice. The materials proposed for discontinuation are listed in Table 3 (page 221). The WHO Catalogue has been updated appropriately (4).

Other activities
The ECBS was informed of discussions that had taken place at a WHO Consultation on International Biological Standards for in vitro Diagnostic Procedures held in September 2000. International biotechnological standardization is becoming increasingly important for the regulation of clinical diagnostic procedures and the consultation was the first occasion when participants from the various disciplines had met together to discuss issues associated with the provision of international reference materials in this area.

Discussion centred on a standardization process, the Draft ISO document 17511, that involves the use of a reference system consisting of a reference material, a reference method and a reference laboratory. The ECBS considered that the draft ISO standard 17511 as presently written may not be entirely applicable to the measurement of complex biological substances in clinical samples, and it recommended WHO collaborate closely with the ISO and other scientific bodies involved in the in vitro diagnostics field. Issues should be resolved whereby the principles of ISO 17511 are maintained as far as possible, while the distinct characteristics and difficulties of biological substances are clearly recognized.

The ECBS endorsed Recommendations arising from a meeting on the standardization and control of serogroup B meningococcal vaccines and agreed that guidelines for outer membrane vesicles-based meningococcal vaccines should now be developed. The ECBS also recommended a review of evidence concerning immune responses to these vaccines and to consider how the assays could best be standardized and reliable immunological correlates of protection established. Finally, it agreed that it would be useful for WHO to set up a working group to consider all aspects of clinical management of meningococcal disease and possibly draft suitable guidance.

In October 1999 in the United Kingdom, a serogroup C conjugate vaccine became the first novel vaccine to be licensed for use in infants for which protective efficacy was not determined by a phase III study, but inferred from immunogenicity data. The ECBS was informed of an expert panel set up to assess current methodologies for measuring immune responses to meningococcal A/C conjugate vaccines and agreed with its recommendation that either human or rabbit serum could be used as the source of complement for the serum bactericidal assay. It also agreed with the criteria proposed to indicate protective human immune responses. However, the ECBS emphasized the need to review these criteria in the light of clinical protection data now emerging from the United Kingdom following the introduction of meningococcal C conjugate vaccine, especially in relation to the demonstration of immunological memory.

Draft Guidelines for the production and control of inactivated oral cholera vaccines were in the preliminary stages of development and were intended to reflect the needs for production and control of the new inactivated oral vaccines, even though further development work will be required. The ECBS recognized that this is a rapidly evolving field of great importance in developing countries. It welcomed and endorsed the action taken by the Secretariat.

A proposed Guidance Document on Viral Inactivation Procedures for Plasma and Plasma-derived Medicinal Products, intended to assure the viral safety of plasma-derived products, was discussed. The document will be circulated to national regulatory authorities less familiar with decontamination processes and will be widely reviewed at a WHO Consultation. A Guide for Good Manufacturing Practices for the Collection of Source Materials for the Production of Plasma Derivatives will be developed to complement the above guidance document, aiming to strengthen the technical capacity and expertise of the national regulatory authorities in the evaluation and control of blood plasma-derived medicinal products.

The ECBS also supported the initiative to develop guidelines on preclinical and clinical testing of vaccines — a project already in progress — and agreed that these Guidelines would be of considerable benefit in supporting national regulations and would serve as guidance for national regulatory authorities and industry, especially in developing countries, and for ethical committees.
Table 1

International biological standards and reference reagents established by the Fifty-first WHO Expert Committee on Biological Standardization

ADDITIONS

**Antigens**
tetanus toxoid (adsorbed) Third International Standard 2000

**Blood products**
fibrinogen concentrate, human First International Standard 2000
Parvovirus B19 DNA, human First International Standard 2000

**Cytokines, growth factors and endocrinological substances**
follicle-stimulating hormone and luteinising hormone, human, urinary, for bioassay Fourth International Standard 2000
somatropin Second International Standard 2000
inhibin B First Reference Reagent 2000

RE-ESTABLISHMENT

insulin-like growth factor 1 for immunoassay First Reference Reagent 1988

CHANGE OF NAME

From: To:
insulin-like growth factor 1 insulin-like growth factor 1 for bioassay (First International Standard 1994)
inhibin, human, recombinant inhibin A, human, recombinant (First International Standard 1994)
alteplase (recombinant tissue plasminogen activator) tissue plasminogen activator (TP A), human, recombinant (Third International Standard 1999)

These substances are held and distributed by the International Laboratory for Biological Standards, National Institute for Biological Standards and Control (NIBSC), Potters Bar, Herts. EN6 3QG, England.

Table 2

Reference materials discontinued by the Fifty-first WHO Expert Committee on Biological Standardization

protamine First International Reference Preparation 1954

References


219
Table 3  
WHO International Reference Preparations proposed for discontinuation at 
the next meeting of the WHO Expert Committee on Biological Standardization

<table>
<thead>
<tr>
<th>Substance</th>
<th>Reference</th>
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<tr>
<td>amykacin</td>
<td>First International Standard 1983</td>
</tr>
<tr>
<td>calcitonin, porcine</td>
<td>Second International Standard 1991</td>
</tr>
<tr>
<td>capreomycin</td>
<td>First International Reference Preparation 1967</td>
</tr>
<tr>
<td>chlortetracycline</td>
<td>Second International Standard 1969</td>
</tr>
<tr>
<td>kininogenase, porcine</td>
<td>First International Standard 1982</td>
</tr>
<tr>
<td>lymecycline</td>
<td>Second International Reference Preparation 1971</td>
</tr>
<tr>
<td>methacycline</td>
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<td>novobiocyn</td>
<td>First International Standard 1965</td>
</tr>
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<td>paromomycin</td>
<td>First International Reference Preparation 1966</td>
</tr>
<tr>
<td>prolactin, ovine</td>
<td>Second International Standard 1962</td>
</tr>
<tr>
<td>thyrotropin, bovine</td>
<td>First International Standard 1983</td>
</tr>
</tbody>
</table>

Comments on this proposal should be forwarded by 30 September 2001 to:  
Dr. E. Griffiths, Quality Assurance and Safety of Biologicals (QSB),  
World Health Organization, 1211 Geneva 27, Switzerland, Fax +41 22 791 4971
General Information

Thirty-second Expert Committee on Drug Dependence

The WHO Expert Committee on Drug Dependence fulfils a fundamental role within the framework of the international drug control system of the UN Conventions. The WHO Expert Committee is entrusted with determining the level of international control to be applied to the medical and scientific evaluation of dependence-producing drugs with a view to providing recommendations to the United Nations Commission on Narcotic Drugs (CND). This is a unique function whereby no drug can be scheduled or controlled internationally without prior evaluation by WHO. The following is an outline of the work undertaken during the Thirty-second meeting of the Expert Committee held in September 2000.

A new review procedure

In 1986, in order to ensure a consistent approach to evaluation, WHO developed a guideline on the formal procedure to be used in the review of dependence-producing psychoactive substances. An updated version of these guidelines was adopted in January 2000 by the WHO Executive Board (1). One major improvement on previous guidelines is the clarification of roles of the 1988 United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1988 Convention) and that of the 1971 Convention on Psychotropic Substances (1971 Convention).

Although WHO is not given any formal role to play in the implementation of the 1988 Convention as such, one of the objectives of the new guidelines is to avoid unnecessary duplication of controls. A particular example of this is discussed below in relation to the scheduling of ephedrine. The successful application of the new guidelines will involve enhanced strengthening and collaboration between WHO and the International Narcotics Control Board (INCB). This latter body holds the mandate to formulate scheduling recommendations with regard to chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances under the 1988 Convention.

Scheduling of ephedrine

During its Thirty-first meeting, the Expert Committee conducted a critical review of ephedrine and recommended that (+)-ephedrine and (-)-ephedrine be placed in Schedule IV of the 1971 Convention (2). However, the UN Commission on Narcotic Drugs (CND) subsequently decided not to vote on this recommendation (3). The Thirty-second meeting conducted a review in accordance with the new guidelines. These provide for the scheduling of a psychotropic substance under the 1971 Convention when that substance is also subject to control as a chemical frequently used in the illicit manufacture of narcotic drugs and psychotropic substances under the 1988 Convention.

The section of the new guidelines applicable to ephedrine states: In the case of a review of a psychoactive substance which is already included in Table I or Table II of the 1988 Convention (such as ephedrine) or has already been recommended by INCB for inclusion therein, the Expert Committee should be guided by three principles. These include the rule that a proposal for a change in the existing status of the substance is to be made when specific new control measures are necessary in order to decrease the extent or likelihood of abuse, while not unduly limiting availability for legitimate medical and scientific purposes.

At the time of the ephedrine review, seven countries reported ephedrine abuse of some significance. However, none of these countries indicated the need for additional control measures, since those introduced in the past have been successfully implemented. The Committee therefore proposed withdrawal of the 1998 recommendation concerning the placement of ephedrine in Schedule IV of the 1971 Convention because WHO has no information to justify recommending international control of ephedrine under the 1971 Convention.

Interpretation guidelines on control status of stereoisomers

Although the Committee had previously rejected a proposed extension of control to isomers, esters, ethers and analogues of psychotropic substances in Schedules I and II of the 1971 Convention, it
now recommended that a phrase be added to Schedule I of the 1971 Convention to clarify the scope of control of stereoisomers. The CND had adopted this recommendation in March 1999 (3).

In addition, with regard to stereoisomers of substances listed in Schedules II through IV of the 1971 Convention, the CND decided that interpretative guidelines should be developed by WHO in collaboration with INCB in order to eliminate any confusion arising from inconsistencies in the present nomenclature. In response to this request, the Committee provided the following guidelines.

1. When the substance listed can exist as stereochemical variants the following should apply:

   (i) if the chemical designation of the substance used in the Convention (or in a subsequent scheduling decision of the CND) does not include any stereochemical descriptors or indicates a racemic form of the substance:

      (a) if the molecule contains one chiral centre, both the \( R \)- and \( S \)-enantiomers and the \( R\text{-}S \)-racemate are controlled, unless specifically excepted by a decision of the CND; and

      (b) if the molecule contains more than one chiral centre, all the diastereoisomers and their racemic pairs are controlled, unless specifically excepted by a decision of the CND.

   (ii) if the chemical designation used in the Convention (or subsequent scheduling decision) for the substance which contains one chiral centre in the molecule includes a stereochemical descriptor indicating a specific enantiomer, the racemic form of the substance is also controlled unless specifically excepted by a decision of the CND.

   (iii) if the chemical designation used in the Convention (or subsequent scheduling decision) for the substance which contains more than one chiral centre in the molecule includes stereochemical descriptors indicating a specific diastereoisomer, only that diastereoisomer is controlled.

2. When one enantiomer is controlled, then a mixture of that enantiomer with the other enantiomeric substance is controlled.

3. The chemical designations and International Nonproprietary Names (INN) used in the scheduling decisions to define substances in Schedules II, III, and IV of the 1971 Convention were considered appropriate at the time such a decision was made. It should be understood that:

   (i) alternative chemical designations constructed according to modified chemical nomenclature rules may be used in official documents as long as they preserve the stereospecificity, when appropriate; and

   (ii) if any subsequent modification of an INN definition uses a chemical designation which is different to that in the scheduling decision, such an INN should be omitted from official documents.

### Scheduling recommendations

Out of the six substances under critical review, the Committee recommended that the following four substances should be controlled under the 1971 Convention.

#### 2C-B (4-bromo-2,5-dimethoxyphenylethylamine)

Despite the limited availability of studies, the chemical and pharmacological similarity of 2C-B to the hallucinogen mescaline has been demonstrated. The altered state of mind induced by hallucinogens such as 2C-B may result in harm to the user and to others. Based on its perceived aphrodisiac effects and known modest abuse potential compared to hallucinogenic drugs in general, it is estimated that 2C-B has a potential for abuse which could constitute a public health and social problem warranting its placement under international control. The Committee noted, however, that hallucinogens are rarely associated with compulsive use and that abuse of 2C-B has been infrequent, suggesting that any abuse is likely to constitute a substantial, rather than a particularly serious risk to public health. Based on these considerations, the Committee recommended that 2C-B be placed in Schedule II of the 1971 Convention.

#### 4-MTA (4-methylthioamphetamine)

4-MTA (4-methylthioamphetamine) is chemically and pharmacologically similar to 4-methoxyamphetamine, MDA and MDMA. 4-MTA is a new synthetic drug which was seized for the first time in 1997. Although evidence of its actual abuse is available only in several countries in Europe, seizures, including those of large quantities reported from a wider range of countries, suggest that the trafficking and abuse of 4-MTA are more widespread than have been reported. Based on this and its similarity to known MDA-type drugs, as well as drug discrimination studies in animals, it is estimated that 4-MTA...
has a potential for abuse which could constitute a public health and social problem and warrant its placement under international control. Taking into consideration that 4-MTA has no recognized therapeutic use and that it has resulted in a number of fatalities, the Committee concluded that abuse of 4-MTA presents an especially serious risk to public health. The Committee therefore recommended that 4-MTA be placed in Schedule I of the 1971 Convention.

GHB (Gamma-hydroxybutyric acid)

Although GHB is an endogenous compound that exists in the human body, it has psychoactive and toxic effects when administered. The pattern and consequences of its abuse in a number of countries in Europe and the USA seem to suggest that its liability for abuse constitutes a significant risk to public health. The current easy availability of GHB and some of its precursors has furthermore contributed to recent reports of abuse. Its wide availability is likely to be reduced once GHB is placed under international control. Based on this situation, the Committee recommended that GHB be placed in Schedule IV of the 1971 Convention.

Zolpidem

Although zolpidem has a somewhat novel neuropharmacological profile relative to classic benzodiazepines, studies suggest that its abuse potential may be comparable. Furthermore, rates of actual abuse and dependence of zolpidem, as well as the risk to public health of abuse, appear to be similar to hypnotic benzodiazepines presently placed in Schedule IV. The Committee therefore recommended that zolpidem be placed in Schedule IV of the 1971 Convention.

Amineptine

Unlike most antidepressants, amineptine elicits CNS stimulation by dopamine uptake blockade. Abuse and/or dependence has been reported from France, Italy, Pakistan and Spain. It has been placed under national control in France. Critical review is recommended as there is a likelihood of amineptine abuse in other countries constituting a significant public health and social problem.

Buprenorphine

is a partial agonist at µ-opioid receptors and an antagonist at κ-opioid receptors. In this respect it is different from prototypical µ-opioid agonists such as morphine and methadone. However, the pattern of diversion and abuse of buprenorphine as reported to INCB indicates its similarity to opiates from an epidemiological point of view. It was also noted that the Committee did not provide in the past an adequate pharmacological explanation about its psychotropic effects nor a clear rationale for the decision to recommend control under the 1971 Convention rather than the 1961 Convention. In consideration of these issues and the increasing rates of abuse and illicit traffic, the Committee recommended critical review of buprenorphine.

Dronabinol

No data are available to demonstrate that individuals are taking dronabinol for non-medical use. The public health problems associated with dronabinol are at present only a potential risk. Dronabinol is not widely available, and diversion or off-label use has not been documented to be significant. Illicit manufacture of dronabinol or ω(omega)-δ(THC) has rarely been reported. Whether synthesized or isolated from the cannabis plant, ω(omega)-δ(THC) is considerably more expensive than its natural preparation (cannabis), thus limiting the likelihood of widespread abuse. In the case of pharmaceutical preparations of dronabinol, the delayed onset and longer duration of action may be additional contributing factors limiting abuse of the product in relation to cannabis. The present scheduling of ω(omega)-δ(THC) is based on the therapeutic usefulness and risk assessment of ω(omega)-δ(THC) made at the Twenty-seventh meeting of the Expert Committee in 1990. The very low rate of actual abuse of ω(omega)-δ(THC) suggests that the risk to public health may actually be less than that required of substances in Schedule II. The Committee therefore recommended a critical review of ω(omega)-δ(THC).
Tramadol

In humans, tramadol has the potential to produce dependence of the morphine-type (µ-opioid). Tramadol is among the top 10 drugs reported for both withdrawal and dependence from data gathered by the WHO International Drug Monitoring Programme, including cases of abuse. Convulsions were reported after the first dose, at the recommended dosage range and at higher doses. Risk of occurrence of convulsions is increased in patients taking concomitant medications that may reduce the seizure threshold, including certain tricyclic compounds and selective serotonin reuptake inhibitors (SSRIs) and with certain medical conditions. The Committee recommended a critical review of tramadol.

References


Regulatory and Safety Matters

Etanercept: serious haematological reactions

European Union — The European Agency for the Evaluation of Medicinal Products (EMEA) has received information of 10 cases of serious blood dyscrasias, some with fatal outcome, in rheumatoid arthritis patients treated with etanercept (Enbrel®).

Etanercept is indicated for active rheumatoid arthritis in adults and active polyarticular-course juvenile chronic arthritis in patients with an inadequate response to methotrexate. Since first marketing, an estimated 80 000 patients have been treated worldwide.

A review has been made of adverse reaction reports and the prescribing and patient information has been modified through a rapid procedure. The following information has been brought to the urgent attention of prescribers:

• Cases of pancytopenia and aplastic anaemia, some with fatal outcome, have been reported rarely (less than 1 in 1000 patients);
• Caution should be exercised in patients with a previous history of blood dyscrasias.
• All patients should be informed of the signs and symptoms suggestive of blood dyscrasias or infections, i.e. persistent fever, sore throat, bruising, bleeding, paleness. They should seek immediate medical advice.
• If blood dyscrasias are confirmed, etanercept should be discontinued.


Infliximab: safety restrictions

European Union — The European Agency for the Evaluation of Medicinal Products (EMEA) has issued a public statement regarding tuberculosis or other opportunistic infections following infliximab (Remicade®) therapy.

Infliximab is a new treatment for patients with rheumatoid arthritis and Crohn disease not responding to established therapies. Infliximab was first approved in 1999 for the treatment of Crohn disease and in February 2000 for rheumatoid arthritis. The manufacturer has since received a number of reports of the onset or reaction of potentially life-threatening tuberculosis infections in treated patients. In many cases these reports have originated in countries with a high incidence of TB and also in patients who have been previously treated with immunosuppressants and/or corticosteroids. In a significant number of cases, the onset of active tuberculosis occurred after three or less infusions of infliximab. However, clinical experience is still limited and long-term effects cannot be ruled out.

Prescribers and patients should be informed of the risk and be especially vigilant for signs of infection throughout treatment. Patients should be evaluated for active and latent tuberculosis before initiation of treatment. If active tuberculosis is suspected, infliximab should be withheld and the risk/benefit for the patient considered.

The product remains useful for the treatment of Crohn disease and rheumatoid arthritis in patients who have not responded to alternative therapies.

Reference:

Phenylpropanolamine withdrawn from drug products

United States of America — Steps have been taken by the Food and Drug Administration to remove phenylpropanolamine from all products because of the risk of haemorrhagic stroke. Manufacturers have been requested to discontinue marketing products containing phenylpropanolamine, which is used as a decongestant in many over-the-counter and prescription cough and cold medications and in weight loss products.
The decision was taken following a review of the Haemorrhagic Stroke Project during a meeting of the Nonprescription Drugs Advisory Committee. The FDA believes that although the risk of haemorrhagic stroke is very low, the conditions for which these products are used do not warrant the increased risk.

Reference: FDA Talk Paper, T00-58, November 2000

Labelling revision for phenylpropanolamine

Japan — The Ministry of Health and Welfare has instructed domestic manufacturers and wholesalers of drugs containing phenylpropanolamine (PPA), a drug linked to haemorrhagic stroke in the United States, to revise the precautions statement of the package insert. This will now list hypertension and a history of cerebral haemorrhage as contraindications while drawing attention to the risk of haemorrhagic stroke.

This action follows a large-scale epidemiological survey conducted in the United States between 1994 and 1999 showing that women who use PPA as an appetite suppressant have a higher incidence of haemorrhagic stroke. The reason is not clear, but is believed to relate to the large doses used.


Phenylpropanolamine advisory to consumers

Canada — Health Canada has issued an advisory concerning phenylpropanolamine (PPA) concerning a reported association with haemorrhagic stroke. PPA is widely used as a nasal decongestant in prescription and non-prescription cough and cold, sinus and combination allergy products.

Although the risk of haemorrhagic stroke is low, it is difficult to predict who is at risk. A public recommendation has been made for consumers not to use any products containing PPA until a full assessment has been completed.

Many of the reports of a suspected link between PPA and haemorrhagic stroke from the United States have been in young women using PPA as an appetite suppressant. However, PPA has not been approved for such use or for weight loss in Canada.


Phenylpropanolamine: strengthening of patient information

United Kingdom — The Committee on Safety of Medicines (CSM) has considered new evidence from the Haemorrhagic Stroke Project. During its meeting on 8 November 2000, it concluded that the evidence of a link between haemorrhagic stroke and phenylpropanolamine (PPA) was weak and associated with uses not licensed in the United Kingdom. Furthermore, over-the-counter cold and influenza remedies on the market in the UK have a lower maximum daily dose (100 mg) than similar products in the United States (1).

However, the debate over safety of phenylpropanolamine may not apply to UK products. In Europe, a different isomer known as norpseudoephedrine is used (2). This consideration of the isomer may explain why many of the adverse drug reactions reported in Europe describe an alteration of mental status whereas those in North America are more often compatible with hypertension.

The CSM has since endorsed this advice and recommended that manufacturers should improve existing product information with more prominent warnings (1). Patients who are concerned about taking products containing PPA should consult their pharmacist, who may suggest alternative remedies. PPA-containing products should not be used by certain groups of patients, such as those with high blood pressure or heart disease.

References

Levacetylmethadol and cardiac disorders

European Union — The European Agency for the Evaluation of Medicinal Products (EMEA) has received information on 10 case reports of life-threatening cardiac disorders including ventricular rhythm disorders such as torsades de pointes in patients treated with levacetylmethadol (Orlaam®).
Levacetylmethadol is indicated for the substitution maintenance treatment of opiate addiction in adults previously treated with methadone. Reports include 5 cases of cardiac arrest, 3 cases of cardiac arrhythmia and 2 cases of syncope. The QT interval was prolonged in 7 of the patients and 4 of these had an episode of torsades de pointes. Three patients required a pacemaker insertion. Life-threatening cases occurred in young patients, a population at low risk of developing these cardiac disorders given the relatively low exposure of the product. As an interim and precautionary measure while a full comparative risk/benefit assessment is made, the following warning has been brought to the attention of prescribers.

- Prescribers are advised not to start any new patients on levacetylmethadol therapy; and
- Patients currently taking levacetylmethadol should contact their doctor for advice regarding their treatment. They must not stop taking levacetylmethadol suddenly without seeking medical advice.

Attention is drawn to the special warnings and precautions already included in the product information for levacetylmethadol.


Bovine-derived materials and vaccines: US recommendations

United States of America — The Center for Biologics Evaluation and Research (CBER) convened a meeting in July 2000 of the Transmissible Spongiform Encephalopathy Advisory Committee and the Vaccines and Related Biological Products Advisory Committee to discuss the status of vaccines which have been manufactured with bovine-derived materials. No evidence exists that cases of variant Creutzfeldt-Jakob disease (vCJD) are related to the use of vaccines, and no cases of vCJD have been reported in the United States.

The Committees concluded that the risk of vCJD posed by vaccines in the United States was theoretical and remote. This conclusion was based on the inherent low risk of the bovine materials involved and/or the dilutions of materials during manufacture. The Committees concluded that the benefits of vaccination outweigh any remote risk of vCJD.

The Food and Drug Administration has requested manufacturers to replace bovine-derived materials obtained from countries where bovine spongiform encephalopathy (BSE) has been reported with materials from BSE-free countries. The Public Health Service recommends that all persons continue to be vaccinated according to current schedules.


Products containing human albumin

Portugal — An evaluation carried out by the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) has concluded that the risk of transmission of variant Creutzfeldt-Jakob disease (vCJD) through blood or human plasma products is highly unlikely.

However, in view of the scarcity of information available on the risk of transmission of vCJD through blood or human plasma products, the Instituto Nacional da Farmácia e do Medicamento (INFARMED) notes that there is no evidence that transmission is impossible. Therefore INFARMED has decided that every medicinal product containing human albumin as an excipient should obtain authorization from INFARMED, batch by batch, before distribution.


Stavudine and didanosine: pregnancy advisory

The manufacturer of stavudine (Zerit®) and didanosine (Videx®) has warned health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed these HIV drugs with other antiretrovirals.

Lactic acidosis occurs when cells of the body are unable to convert food into usable energy. As a result, excess acid accumulates in the body and vital organs may be damaged. Severe lactic acidosis is an infrequent, but documented complication of nucleoside analogues. Pancreatitis is also a complication of stavudine and didanosine.
This new warning follows three reported cases of fatal lactic acidosis that occurred in pregnant women taking a combination of drugs to treat HIV. Several nonfatal cases of pancreatitis with or without lactic acidosis or hepatic failure have occurred in pregnant women receiving stavudine plus didanosine. It is unclear whether pregnancy potentiates these adverse effects.

The manufacturer recommends that the combination of the two drugs should be prescribed to pregnant women only when the potential benefit clearly outweighs the potential risk. For example, when other treatment options have been exhausted.

The Food and Drug Administration has strengthened the black box warning to include this new prescribing information. Patients receiving the combination should be closely monitored since this syndrome may develop abruptly and in the absence of abnormal laboratory values. Health care professionals should maintain a high index of suspicion in monitoring these patients and are encouraged to report any adverse effects.


Methysergide and cardiac valvulopathy

Australia — Methysergide is an ergot alkaloid used in the prophylaxis of migraine. Its most serious known adverse effect is retroperitoneal fibrosis. It has also been reported to be associated with fibrotic changes to other organs including heart valves. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received two recent reports describing cardiac valvulopathy.

The prescribing information for methysergide states that continuous administration of the drug should not exceed 6 months and then should be withdrawn for 3–4 weeks before recommencement. Of particular interest in the two ADRAC reports was that the cardiac abnormalities occurred despite interrupted treatment according to directions.

The valve damage reported appears to be similar to that with cases of carcinoid syndrome, use with ergotamine and, more recently, fenfluramine. Many of these reports describe the presence of a white surface plaque on the valves. These observed similarities suggest that a common factor may be causing the damage and may be related to the action of excess serotonin.

Prescribers should be aware that although methysergide drug holidays are generally recommended to prevent fibrotic changes, these changes can still occur and may affect cardiac valves.


Greater control for cisapride

United Arab Emirates — After studying reports of rare but serious ventricular arrhythmias caused by the gastrointestinal motility drug cisapride, the UAE Ministry of Health has made cisapride a Registered Prescription (RP) drug. An RP drug can only be prescribed using a special duplicate and numbered prescription with details recorded and forwarded to the Ministry of Health. This allows complete follow up of all users. Severe penalties are in place for any pharmacist who supplies an RP drug without the correct prescription.

The UAE decision recognizes that cisapride remains a unique drug and that some patients may not be able to use alternatives. These control measures are meant to ensure that only specialists will prescribe the drug.


New combination drug for HIV

United States of America — The Food and Drug Administration (FDA) has approved Trizivir® alone or in combination with other antiretroviral agents, for the treatment of HIV infection in adults and adolescents. Trizivir® is a combination of three synthetic nucleoside analogues previously approved by the FDA: abacavir, lamivudine, and zidovudine. Benefits relate to the requirement for only one tablet twice daily which is expected to improve adherence to treatment.

In clinical studies of abacavir, about 5% of patients developed hypersensitivity reactions that can be serious or fatal. These include fever, skin rash, fatigue, gastrointestinal symptoms, pharyngitis, dyspnoea and cough. Rechallenge is contraindicated. Other possible effects include lactic acidosis, liver reactions, anaemia, neutropenia, nausea, fatigue and myopathy.

Tacrolimus for atopic dermatitis

United States of America — The Food and Drug Administration has approved a new treatment for eczema, tacrolimus ointment 0.1% and 0.03% for adults and 0.03% for children 2 years and under. It is indicated for patients with moderate to severe eczema who are intolerant of standard therapies.

Common side effects associated with tacrolimus are temporary stinging or burning sensation on application. The adverse effects of ultraviolet light on the skin may be accentuated. It is therefore important for patients to avoid sunlight, UVA or UVB light.


Letrozole approved for advanced breast cancer

United States of America — The Food and Drug Administration has approved letrozole (Femara®) as a first-line treatment for postmenopausal women with hormone receptor positive or hormone receptor unknown, advanced or metastatic breast cancer. Letrozole, an aromatase inhibitor, was previously approved for cancer which had not responded to anti-estrogen drugs.

In a randomized, double-blind, multinational trial of over 900 postmenopausal women, letrozole was shown to be more effective than tamoxifen by providing patients with a median of 3.6 more months before tumours worsened. The incidence of adverse effects in the study was similar for the two drugs with the most frequently reported adverse effects including bone pain, hot flushes, back pain, nausea, arthralgia and dyspnoea.


Alosetron withdrawn

United States of America — The manufacturer of alosetron (Lotronex®), has informed the Food and Drug Administration (FDA) that it has voluntarily withdrawn this product from the market (1). Alosetron is a prescription medication approved to treat irritable bowel syndrome in women (2). The FDA is advising patients taking alosetron to contact their healthcare providers to discuss treatment alternatives.

The FDA has been concerned about reported cases of intestinal damage resulting from reduced blood flow to the intestine (ischaemic colitis) and severely obstructed or ruptured bowels (complications of severe constipation). Post-marketing reports of serious adverse events, included 5 reports of death. As of 10 November 2000, the FDA has received and reviewed a total of 70 cases of serious post-marketing adverse events, including cases of ischaemic colitis and severe constipation. Of the 70 cases, 34 resulted in hospitalization without surgery, 10 resulted in surgical procedures, and 3 resulted in death. The FDA has received two additional reports of death that the agency did not classify as being cases of ischaemic colitis or severe complications of constipation.

References:

Basiliximab: hypersensitivity reactions

The manufacturer of basiliximab (Simulect®), has informed health care providers of 17 cases of severe acute hypersensitivity reactions, including anaphylaxis, occurring in patients following the administration of basiliximab. The onset of reactions occurred within 24 hours following initial exposure and/or following re-exposure.

Labelling recommends that medications for the treatment of severe hypersensitivity reactions, including anaphylaxis, are available for immediate use and that the second dose of basiliximab is withheld if a hypersensitivity reaction occurs. The labelling for basiliximab has been revised to reflect this new information.

Healthcare professionals are urged to report all serious adverse events suspected to be associated with the use of basiliximab to the manufacturer or the relevant authority.

**Budipine: cardiac reactions**

**Germany** — The manufacturer of the antiParkinson agent, budipine (Parkinsan®), has revised the contraindications in the product information to include patients with cardiomyopathy, myocarditis and AV block II and III as well as patients with a history of ventricular arrhythmia, especially tachycardia (torsades de pointes). This action was taken by the Federal Institute for Drugs and Medical Devices which found that the incidence of cardiac adverse reactions was not adequately reflected in the product information.

In addition, doctors are advised that an electrocardiogram should be performed before the start of therapy, and again one to three weeks afterwards and on increase of the dosage. With regard to risk factors for electrolyte imbalance, laboratory tests should be performed. If symptoms such as palpitations, dizziness or syncope appear, budipine should be withdrawn and the patient examined for QT-prolongation.


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**Capecitabine: revised data sheet**

The manufacturer of the antineoplastic drug, capecitabine (Xeloda®), has informed prescribers of important safety-related changes to the labelling to include contraindications in patients with severe renal impairment. In addition, for patients with moderate renal impairment, the starting dose of capecitabine should be reduced.

Updated data indicate that patients with moderate or severe renal impairment had a high rate of grade 3-4 serious adverse events. The increased incidence of undesirable effects did not impact negatively on the overall benefit for these patients when treated with capecitabine since the tumour response rate was maintained. Patients with mild renal impairment, although experiencing slightly more serious adverse events and withdrawals than normal, maintained their overall benefit/risk ratio.


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**Benzathine penicillin: fatal mega-unit injections**

**Zimbabwe** — The Medicines Control Authority has received 3 reports of death associated with benzathine penicillin injections from 3 different manufacturers.

Prior to these reports — from 1993 to 1999 — the Authority has received only one report of an adverse reaction associated with benzathine penicillin injection where a patient had fainted for about 30 seconds after administration of the injection, but recovered. No concomitant medicines were taken. It was also reported that the patient had suffered a previous adverse reaction following a penicillin injection.

It is not clear whether these cases represent a higher incidence of hypersensitivity than would normally be expected with this drug.


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**Disulfiram: hepatic reactions**

**Sweden** — Disulfiram is prescribed as an adjunct in the treatment of chronic alcoholism inhibiting the enzyme, aldehyde dehydrogenase. The combination of alcohol and disulfiram leads to an accumulation of acetaldehyde which induces classic symptoms such as flushing of the face, tachycardia, dyspnoea, nausea and vomiting.

Disulfiram may also cause severe liver injuries. In the Swedish Drug Reference List (FASS), liver damage is labelled as “a rare adverse reaction (<1/1000), usually with similar symptoms as for acute hepatitis and/or icterus as well as increased levels of SGOT and SGPT and bilirubin”. This effect may be an allergic as well as toxic reaction.

In the Swedish adverse drug reactions register, SWEDIS, 149 case reports associated with disulfiram have been received since 1971. Of these reports there are 157 adverse reactions in total, of which 63 cite liver and biliary system disorders. Out of these 63 reports, seven have been classified as serious. The duration of treatment varied from five weeks to three months before onset of the reaction.
In three of these cases, the patients also took other drugs: sertraline, paroxetine and venlafaxine. These drugs may also be implicated in the reaction.

In three cases of severe liver damage with fatal outcome, disulfiram was suspected to have caused the reaction. If signs of liver damage should appear, it is recommended that disulfiram be discontinued and liver tests performed.


Isoniazid and rifampicin: severe skin reactions

Zimbabwe — The Medicines Control Authority has recently received four adverse reaction reports of “burn-like lesions on the whole body and mucosal ulcerations” associated with isoniazid and rifampicin. None of the four patients were taking concomitant medicines. All patients recovered.

It was noted from records at the WHO Collaborating Centre for International Drug Monitoring that since 1993 the Authority had received seven reports of skin reactions (rash, pruritus) associated with rifampicin and isoniazid. Five of the seven reports indicated that the patients were also taking ethambutol and pyrazinamide.


Omeprazole-induced interstitial nephritis

New Zealand — Acute renal impairment caused by interstitial nephritis is a rare complication of treatment with omeprazole. The New Zealand Centre for Adverse Reaction Monitoring (CARM) has received 7 reports of acute renal failure due to interstitial nephritis associated with omeprazole. While omeprazole use was being monitored, two reports of interstitial nephritis were received from a total cohort of 22 050 patients. There were several other reports of renal failure.

Recognition of interstitial nephritis may be difficult because the symptoms of renal impairment are non-specific and diagnosis of renal dysfunction can only be made by carrying out biochemical tests. In general, the presenting features described for interstitial nephritis are fever, rash and eosinophilia but these features are not always seen.

Interstitial nephritis may be caused by infection, autoimmunity and glomerular disease as well as hypersensitivity to medicines, particularly antibacterials and nonsteroidal anti-inflammatory agents. The medicines most commonly implicated are methicillin, penicillin, sulphonamides, co-trimoxazole, cefalosporins, rifampicin, fenoprofen, mefenamic acid, allopurinol, phenytoin and thiazides. There are no known reports of death as a result of this adverse reaction. In four of the published cases, renal function deteriorated again when omeprazole was reintroduced.

Patients taking omeprazole, or any of the medicines listed above, who present with symptoms and signs of hypersensitivity should be withdrawn pending nephrology assessment.


Ozagrel sodium: kidney function disorder

Japan — Ozagrel sodium, a thromboxane synthesis enzyme inhibitor is indicated for the improvement of postoperative cerebrovascular contraction and accompanying cerebral ischaemia and for improvement of motility disturbance due to acute cerebral thrombosis.

In April 1994 and April 1996, abnormal kidney function, increase of BUN, and increase of creatinine were added to the labelling. However, 14 serious cases of acute renal failure have since been reported to the Ministry of Health and Welfare. Manufacturers have accordingly been directed to include “abnormal renal function” in the product labelling.


Drug information to the public

Japan — The Health Policy Bureau of the new Ministry of Health, Labour and Welfare plans to create a council responsible for the provision of easy-to-understand information to the general public on indications, adverse reactions, and prices of drugs on the Japanese market.
The council will be created in response to the price system reforms decided at the end of 1999. The policy calls for systems making it possible to supply comparable drug information to the general public. The council will have about 15 members, including representatives of drug manufacturers and wholesalers. It will evaluate the use of new technologies, especially those used by drug companies, to disseminate information effectively. The council will also deal with a discrepancy in existing laws. At present, the Pharmaceutical Affairs Law controls the supply of information through the Internet as advertisements, while information to medical institutions remains uncontrolled because such information is not considered to be an advertisement.


Northern hemisphere influenza vaccine composition

World Health Organization — The composition for the northern hemisphere influenza season (2001-2002) has been decided and communicated to vaccine manufacturers. It is recommended that the influenza vaccine should contain the following three components:

- An A/Moscow/10/99 (H3N2)-like virus (A/Panama/2007/99 is this kind of virus).
- An A/New Caledonia/20/99 (H1N1)-like virus.

WHO strongly recommends the use of vaccine as an effective preventive measure against this potentially fatal disease. About 50 - 80% of vaccine recipients will be protected against the disease when there is a good match between the vaccine and strains of circulating influenza virus. However, in those cases where the vaccine does not fully protect against influenza, severity of illness and frequency of complications are reduced.

Most populations have been previously exposed to influenza A(H3N2), influenza A(H1N1) and B viruses and are known to have some degree of residual immunity. One dose of influenza vaccine should therefore be sufficient for all ages except young children. Previously unimmunized children should receive two doses of vaccine at an interval of at least four weeks.

The specific vaccine viruses used in each country should be approved by the national control authorities who are responsible for making recommendations on their use.

ATC/DDD Classification (final)

The following final anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place in March 2000 in Geneva. They came into force on 1 August 2000 and can be viewed on http://www.whocc.nmd.no. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

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</tr>
<tr>
<td>macrogol</td>
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<td>A06AD15</td>
</tr>
<tr>
<td>melanoma vaccine</td>
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<td>L03AX12</td>
</tr>
<tr>
<td>nateglinide</td>
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</tr>
<tr>
<td>nitisinone</td>
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<td>A16AX04</td>
</tr>
<tr>
<td>octenidine, combinations</td>
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<td>D08AJ57</td>
</tr>
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<td>octenidine, combinations</td>
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<td>pranoprofen</td>
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<tr>
<td>sodium fluoride, combinations</td>
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<td>technetium (99mTc) sulesomab</td>
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<td>verteporfin</td>
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ATC code changes
Previous: disulfiram V03AA01
New: disulfiram N07BB01
Previous: calcium carbimide V03AA02
New: calcium carbimide N07BB02
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<tr>
<th>ATC level</th>
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<th>ATC code</th>
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<tbody>
<tr>
<td>Previous:</td>
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</tr>
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<td>New:</td>
<td>acamprosate</td>
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<tr>
<td>Previous:</td>
<td>naltrexone</td>
<td>V03AB30</td>
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<tr>
<td>New:</td>
<td>naltrexone</td>
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<tr>
<td>Previous:</td>
<td>levacetylmethadol</td>
<td>N02AC06</td>
</tr>
<tr>
<td>New:</td>
<td>levacetylmethadol</td>
<td>N07BC03</td>
</tr>
<tr>
<td>Previous:</td>
<td>methadone</td>
<td>N02AC02</td>
</tr>
<tr>
<td>New:</td>
<td>methadone</td>
<td>N07BC02</td>
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</table>

**Change of level name**

Previous: Antismoking agents
New: Drugs used in addictive disorders
Previous: Antismoking agents
New: Drugs used in nicotine dependence
Previous: Oxytocin and derivatives
New: Oxytocin and analogues

**New DDDs:**

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>DDD</th>
<th>Unit</th>
<th>Route of Administration</th>
<th>ATC code</th>
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<tbody>
<tr>
<td>amodiaquine</td>
<td>0.5</td>
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<td>O</td>
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<td>artemether</td>
<td>0.28</td>
<td>g</td>
<td>O</td>
<td>P01BE02</td>
</tr>
<tr>
<td>artemisinin</td>
<td>1</td>
<td>g</td>
<td>O</td>
<td>P01BE01</td>
</tr>
<tr>
<td>artenimol*</td>
<td>0.28</td>
<td>g</td>
<td>O</td>
<td>P01BE05</td>
</tr>
<tr>
<td>artesunate</td>
<td>0.28</td>
<td>g</td>
<td>O</td>
<td>P01BE03</td>
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<tr>
<td>dihydroemetine</td>
<td>60</td>
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<td>P01AX09</td>
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<td>exemestane</td>
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<td>O</td>
<td>L02BG06</td>
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<td>galantamine</td>
<td>24</td>
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<td>halofantrine</td>
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<td>g</td>
<td>O</td>
<td>P01BX01</td>
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<tr>
<td>ibandronic acid</td>
<td>4</td>
<td>mg</td>
<td>P**</td>
<td>M05BA06</td>
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<tr>
<td>leflunomide</td>
<td>15</td>
<td>mg</td>
<td>O</td>
<td>L04AA13</td>
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<tr>
<td>macrogol***</td>
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<td>g</td>
<td>O</td>
<td>A06AD15</td>
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<td>mercaptamine</td>
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<td>pioglitazone</td>
<td>30</td>
<td>mg</td>
<td>O</td>
<td>A10BG03</td>
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<tr>
<td>risedronic acid</td>
<td>30</td>
<td>mg</td>
<td>O</td>
<td>M05BA07</td>
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<td>tirotaban</td>
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<td>zotepine</td>
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<td>O</td>
<td>N05AX11</td>
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</tbody>
</table>

*Previous name: dihydroartemisinin
**Course dose
***Refers to macrogol 4000
The following temporary anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 23 and 24 October 2000. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, e-mail: whoccc@nmd.no. If no objections are received, the new ATC codes and DDDs will be considered final and will be included in the January 2002 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

<table>
<thead>
<tr>
<th>ATC level</th>
<th>INN/common name</th>
<th>ATC code</th>
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</thead>
<tbody>
<tr>
<td>New ATC level codes (other than 5th level):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs acting on serotonin receptors</td>
<td>alosetron</td>
<td>A03AE01</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>benzethonium chloride, combinations</td>
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<tr>
<td>Streptogramins</td>
<td>betacarotene</td>
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<td></td>
<td>betaine</td>
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</tr>
<tr>
<td></td>
<td>betamethasone</td>
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<tr>
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<td>biphenylol</td>
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<tr>
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<td>bisacodyl, combinations</td>
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<tr>
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<td>carglumic acid</td>
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<td>caspofungin</td>
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<td>doxycycline</td>
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<tr>
<td></td>
<td>drosiprone and estrogen</td>
<td>G03AA12</td>
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<tr>
<td></td>
<td>dyclonine</td>
<td>R02AD04</td>
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<tr>
<td></td>
<td>dydrogesterone and estrogen</td>
<td>G03FA14</td>
</tr>
<tr>
<td></td>
<td>epinephrine</td>
<td>R01AA14</td>
</tr>
<tr>
<td></td>
<td>ethanol</td>
<td>D08AX08</td>
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<tr>
<td></td>
<td>indium (111In) capromab pendetide</td>
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<td></td>
<td>ioxilan</td>
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<td>iprocoxib</td>
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<td>levetiracetam</td>
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<td>linezolid</td>
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<td>lopinavir</td>
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<tr>
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<td>magnesium citrate</td>
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<td>magnesium oxide</td>
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<td>nifedipine</td>
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<td>peginterferon alfa-2a</td>
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<td>phenol</td>
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<td>pyrithione zinc</td>
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<tr>
<td></td>
<td>quinupristin/dalfopristin</td>
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### New ATC 5th level codes (continued):

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<tr>
<td>tegaserod</td>
<td>A03AE02</td>
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<tr>
<td>tramadol, combinations</td>
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<tr>
<td>unoprostone</td>
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<tr>
<td>zoledronic acid</td>
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### ATC code changes

<table>
<thead>
<tr>
<th>Previous</th>
<th>New</th>
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<tr>
<td>bupropion</td>
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<td>glatiramer acetate</td>
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<tr>
<td>latanoprost</td>
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<tr>
<td>pristinamycin</td>
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<tr>
<td>pristinamycin</td>
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### Change of name:

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<th>New</th>
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<td>Macrolides and lincosamides</td>
<td>Macrolides, lincosamides and streptogramins</td>
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<td>amfebutamone</td>
<td>bupropion N07BA02</td>
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### New DDDs:

<table>
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<tr>
<th>INN/common name</th>
<th>DDD</th>
<th>Unit</th>
<th>Route of Administration</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>alosetron*</td>
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<td>O</td>
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<td>atosiban</td>
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<td>ml</td>
<td>P</td>
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<tr>
<td>bupropion**</td>
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<td>O</td>
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<td>dihydrocodeine</td>
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<td>O</td>
<td>N02AA08</td>
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<td>O</td>
<td>A02BC05</td>
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<tr>
<td>etanercept</td>
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<td>infliximab</td>
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<td>U</td>
<td>P</td>
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<td>P</td>
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<td>O</td>
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</tr>
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<td>zoledronic acid*</td>
<td>4</td>
<td>mg</td>
<td>P</td>
<td>M05BA08</td>
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* Temporary ATC code
** Temporary changed ATC code from N06AX12 to N07BA02
Herbal Medicines

Research and evaluation of traditional and herbal medicines

The expanding use of traditional and herbal medicines is gaining recognition globally. Not only do herbal medicines continue to be used in primary health care in developing countries, but they are also increasingly popular in those countries where conventional medicine is predominant. With this expansion in use beyond national boundaries, the safety, efficacy and quality control of herbal medicines and traditional therapies have become important concerns for health authorities and the public. The difficulty of regulation is particularly challenging given the development of traditional medicine by different cultures in different regions in the absence of a parallel development of international standards and appropriate methods of evaluation.

Consequently, governments, researchers and manufacturers are increasingly in need of standards, technical guidance and information to assist them in determining how research and evaluation of traditional and herbal medicines should be carried out. Since 1991, WHO has published a series of technical guidelines on traditional medicine which are particularly relevant to current needs. WHO’s latest document in the series, General Guidelines for Methodology on Research and Evaluation of Traditional Medicine,* has been developed as a comprehensive guide to methodologies to be used when carrying out research involving the use of herbal medicines and traditional procedure-based therapies.

It includes sections on research and evaluation of herbal medicines and traditional procedure-based therapies, clinical research, and related issues such as ethics, education, training and surveillance. The following text has been adapted from the guidelines.

The methodologies for research and evaluation of traditional medicine should guarantee the safety and efficacy of herbal medicines and traditional procedure-based therapies without becoming obstacles to the application and development of traditional medicine generally.

Methodologies for research and evaluation

Traditional medicine involves the use of herbal medicines, animal parts and minerals. However, herbal medicines are the most widely used of the three. The General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine cover a wide range of issues and are intended to meet the different situations that exist in various countries and regions of the world. The guidelines can be modified to meet the specific needs of countries. Where appropriate, a phased approach to the implementation of the guidelines should be considered. They are intended particularly to serve as a reference source for researchers, health care providers, manufacturers, traders, and health authorities.

Definitions

Certain definitions concerning herbal medicines are set out in the Guidelines for the Assessment of Herbal Medicines (1) and Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines (2). In order to make WHO definitions consistent, certain terms have now been harmonized to meet the demand for the establishment of standard, internationally accepted definitions for use in the evaluation and research of herbal medicines.

Herbs

Herbs include crude plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.

*General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine. World Health Organization, WHO/EDM/TRM/2000.1. The guidelines have been formulated in collaboration with national drug regulatory authorities and scientists from many countries worldwide, members of the WHO Expert Advisory Panel on Traditional Medicine and WHO Collaborating Centres on Traditional Medicine. A WHO informal consultation on Research Methodology for Evaluation of Traditional Medicine, was held at the National Institutes of Health in the United States, in 1997 prior to drafting of the document, which was later finalized at a WHO consultation, Hong Kong SAR, China in April 2000.
Herbal materials
Herbal materials include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other materials.

Herbal preparations
Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.

Finished herbal products
Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term mixture herbal product can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal.

Traditional use of herbal medicines
Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products, that contain as active ingredients parts of plants, or other plant materials, or combinations. Traditional use of herbal medicines refers to the long historical use of these medicines. Their use is well established and widely acknowledged to be safe and effective, and may be accepted by national authorities.

Therapeutic activity
Therapeutic activity refers to the successful prevention, diagnosis and treatment of physical and mental illnesses; improvement of symptoms of illnesses; as well as beneficial alteration or regulation of the physical and mental status of the body.

Active ingredients
Active ingredients refer to ingredients of herbal medicines with therapeutic activity. In herbal medicines where the active ingredients have been identified, the preparation of these medicines should be standardized to contain a defined amount of the active ingredients, if adequate analytical methods are available. In cases where it is not possible to identify the active ingredients, the whole herbal medicine may be considered as one active ingredient.

Botanical verification and quality considerations
The first stage in assuring the quality, safety and efficacy of herbal medicines is identification of the plant species by botanical verification. The information required includes the currently accepted Latin binomial name and synonyms, vernacular names, the parts of the plant used for each preparation, and detailed instructions for agricultural production and collection conditions according to each country’s good agricultural practice. Detailed information is presented in WHO Quality Control Methods for Medicinal Plant Materials (3) and WHO Monographs on Selected Medicinal Plants (4).

Research and evaluation of safety and efficacy
Research and evaluation of herbal medicines that do not have a long history of use or which have not been previously researched, should follow WHO’s Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines (2). For herbal medicines with a well-documented history of traditional use, the following procedures may be followed.

Literature review
In assessing the safety and/or efficacy of a herbal medicine, whether derived from a single plant or from a defined mixture of plants, the first step involves the evaluation of literature reports. The literature search should be made using reference books, review articles, systematic surveillance of primary sources, and/or database searches. If it is felt that reference books and review articles might contain inaccurate information, primary references should be consulted for in-depth analysis. The search profile used should then be recorded and the search be extended to gather information on closely related plant species for chemotaxonomic correlation.

If several investigators publish similar safety and/or efficacy data, they should be accepted as useful indicators. In vitro biochemical or cellular safety data should be viewed as indicators of potential toxicity, but not as absolute markers. In vivo data from animal studies are more indicative of toxicity.
and may be considered to be safety markers. For both safety and efficacy, a pharmacological effect observed in vitro or in animal models is not necessarily applicable to humans. In vitro data usually serve to verify the reported mechanism of action in animals or humans. Such data have to be confirmed by clinical studies. Well-documented reports of pharmacological activity in animals or humans may be viewed as having scientific rationale.

**Theories and concepts of systems of traditional medicine**

The theories and concepts of prevention, diagnosis, improvement and treatment of illness in traditional medicine may rely on a holistic approach towards the sick individual, and disturbances will also be treated on the physical, emotional, mental, spiritual and environmental levels simultaneously. As a result, most systems of traditional medicine may use herbal medicines or traditional procedure-based therapies along with certain behavioural rules promoting healthy diets and habits. Holism is a key element of all systems of traditional medicine. Therefore, when reviewing the literature on traditional medicine (both herbal medicines and traditional procedure-based therapies), the theories and concepts of the individual practice of traditional medicine, as well as the cultural background of those involved, must be respected.

**Review of safety and efficacy literature**

A review of the literature should identify the current level of evidence for the safe and effective use of a herbal medicine. In cases where the traditional uses and experience of a herbal medicine in humans have not established its safety and efficacy, new clinical studies will be necessary. If well-known herbal medicines are formulated into a new mixture, however, the requirements for proof of safety and efficacy should take into account the established uses of each herbal medicine. Such information may appear in authoritative national documents such as pharmacopoeias or official guidelines of national authorities, or in scientific publications. However, it should not be forgotten that new preparative methods may alter the chemical, toxicological and even pharmacological profiles of traditionally used herbal medicines.

**Safety**

Reported and documented side-effects that have been recorded according to established principles of Pharmacovigilance of a herb or herb mixture, its closely related species, constituents of the herb and its preparations/finished herbal products should be considered when decisions are made about the need for new pharmacological or toxicological studies.

The absence of any reported or documented side-effects is not an absolute assurance of safety for herbal medicines. However, a full range of toxicological tests may not be necessary. Tests which examine effects that are difficult or even impossible to detect clinically should be encouraged. Suggested tests include immunotoxicity, genotoxicity, carcinogenicity and reproductive toxicity.

When there is no documentation of historical use of a herbal medicine, or when doubts exist about its safety, additional toxicity studies should be performed. Where possible, such studies should be carried out in vitro. Using in vitro tests can reduce the number of in vivo experiments. If in vivo studies are needed, they are to be conducted humanely, with respect for the animals’ welfare and rights. Toxicity studies should be conducted in accordance with generally accepted principles, such as those described in WHO’s Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines (2).

**Efficacy**

It is important for herbal medicines, and particularly for those made from a mixture of herbal products, that the requirements for proof of efficacy, including the documentation required to support the indicated claims, should depend on the nature and level of the indications. For the treatment of minor disorders, for non-specific indications, or for prophylactic uses, less stringent requirements (e.g. observational studies) may be adequate to prove efficacy, especially when the extent of traditional use and the experience with a particular herbal medicine and supportive pharmacological data are taken into account.

The level of the evidence and the grading of recommendations must correspond to the nature of the illness to be treated or the nature of the physical or mental function to be influenced and regulated. Definitions of levels of evidence and the grading of recommendations from the USA Agency for Health Care Policy and Research may be used for guidance (5). Many other national documents, such as the Australian guidelines for levels and kinds of evidence to support claims for therapeutic goods (6) will also provide a reference.
The therapeutic alternatives available within the community and the risks of the herbal in question have to be taken into account. It should be noted that in the case of herbal medicines made from herb mixtures, a therapeutic or scientific rationale must exist for the presence of each herb in the mixture. Research studies on the possible therapeutic effects of herbal medicines made from herb mixtures or specific combinations of herbs, however, need to be conducted.

**Clinical studies**

The scope and design of such studies should be based on information of traditional use obtained from official national compendia and relevant literature, or by consultation with traditional medical practitioners.

In the case of a new herbal medicine, a new indication for an existing herbal medicine, or a significantly different dosage form or route of administration, the general principles and requirements for a clinical trial should follow as closely as possible to those which apply to conventional drugs, such as guidelines for good clinical practice (7–8). In some cases, however, the design of such studies must be adapted to deal with the particularities of herbal medicines.

Well-established, randomized controlled clinical trials provide the highest level of evidence for efficacy. Such studies facilitate the acceptance of herbal medicines in different regions and in people with different cultural traditions. However, methods such as randomization and use of a placebo may not always be possible as they may involve ethical issues as well as technical problems. For example, it may not be possible to have a placebo control if the herbal medicine has a strong or prominent smell or taste, as is the case for products containing certain essential oils. In addition, patients who have been treated previously with the herbal medicine under investigation with a characteristic organoleptic property, cannot be randomized into control groups. In the case of herbal medicines with a strong flavour, placebo substances with the same flavour may have a similar function. In such cases, it may be advisable to use a low dosage of the same herbal medicine as a control.

Observational studies involving large numbers of patients may also be a very valuable tool for the evaluation of herbal medicines. According to the theories and concepts of traditional medicine, the prevention, diagnosis, improvement and treatment of illness is often based on the specific needs of the individual patient. Therefore, single-case studies for the evaluation of efficacy of a herbal medicine should not be ignored.

Regulatory requirements of national authorities for evaluating herbal medicines differ from country to country. Many governments have recently developed their own national regulations for traditional medicine. For an extensive review of the regulatory situation in various countries, consult WHO’s Regulatory Situation of Herbal Medicines: a Worldwide Review (9).

**Research**

Normally, clinical research of all types of conventional and traditional medicine considers both efficacy and safety, and is conducted in line with WHO’s Guidelines for Good Clinical Practice and the Declaration of Helsinki (7).

The infrastructure for research in traditional medicine is significantly less developed than that for conventional medicine. However, there is now an increasing demand that the safety and efficacy of traditional medicine be determined so that it can be considered by the public. In the development of traditional medicine, it is important that support be given to the establishment of appropriate infrastructures.

Other pragmatic issues that require consideration include funding, facilities, and involvement of properly trained research personnel and traditional medical practitioners. Clinical research must be carried out under conditions which ensure adequate safety for the subjects. The institution selected must have adequate facilities, including laboratories and equipment, where necessary, and sufficient clerical, medical and allied health workers to support the study as required. Facilities should be available to meet any emergencies.

If a multicentre study is necessary, this may require a special administrative system to ensure that the study is conducted simultaneously and adequately at different sites by several investigators following the same protocol. It will be necessary to train investigators from different sites to follow the same protocol, and to standardize methods of patient selection, termination of patient participation, administration, and data collection and evaluation. Appropriate consultation about the statistical analysis is necessary during the planning, execution and assessment phases to ensure methodological consistency.
Ethics
The CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (10) should be implemented in each clinical trial. An institutional or national ethics committee should review each trial.

Education and training
All health care providers of traditional medicine should be encouraged and required to have proper training in both traditional and conventional medicine, as their training and skills will affect the safety and efficacy of the treatment. The practitioners’ knowledge and skills need to be continuously upgraded to enable them to engage in clinical research within their own individual specialty.

Surveillance systems
According to the situation of traditional medicine in a particular country, governments may need to establish national surveillance systems at different levels of the health sector to monitor and evaluate any adverse effects of herbal medicines. Knowledgeable researchers and practitioners of traditional medicine should be consulted during the development of such systems.

The evaluation of adverse effects needs to be based on appropriate methods of determining causality. Such methods include instruments to determine adverse events experienced by target groups (patients and practitioners), prospective and retrospective studies to determine adverse effects in specific settings, and post-marketing surveillance of herbal medicines.

References and further reading

The safety of herbal medicines
The use of herbal medicines poses sensitive challenges to drug regulatory authorities responsible for the safety, efficacy and quality of medicines both nationally and internationally. An informative presentation on these issues was made by the WHO Programme on Traditional Medicines at the Twenty-third Annual Meeting of National Centres participating in the WHO International Drug Monitoring Programme held in Tunisia in November 2000.

The use of medicinal plants is accepted as the most common form of traditional medicine. Among the entire flora, it is estimated that 35 000 to 70 000 species have been used for medicinal purposes. Some 5000 of these have been studied in biomedical research. In developing countries, herbal medicines continue to play an important role in primary health care, especially where coverage of health services is limited. In industrialized countries, herbal medicines are increasingly popular. However, the expanded use of herbal medicines has led to concerns relating to assurance of safety, quality and efficacy. The four major steps to overcome concerns have been identified as:

- Regulation and registration of herbal medicines.
- Quality control of herbal medicines and materials.
- Rational use.
- National surveillance systems to monitor and evaluate adverse reactions.
The regulatory situation differs from country to country and herbal medicines may be classified as prescription only, proprietary drug products, food supplements or foods, although, in general, the majority of herbal medicines have no regulatory status. It is therefore important that the manufacture of herbal medicines and related products moving in international commerce needs to be governed by similar standards of safety, quality and efficacy as those required for pharmaceutical products. In this respect, proof of safety should always take precedence over establishment of efficacy.

In order to facilitate the development of national regulation and registration of herbal medicines, WHO has published a Regulatory Situation of Herbal Medicines: a Worldwide Review containing regulatory information from 50 countries (1). WHO has also published Guidelines for the Assessment of Herbal Medicines (2) and General Guidelines on Methodologies for Research and Evaluation of Traditional Medicine to assist countries in the evaluation of herbal medicines (3).

Quality will influence safety, and often depends on the quality of the raw materials employed. A review of published adverse drug reactions of herbal medicines has identified the main cause of such events to be contamination and adulteration. Quality assurance is vital (4). WHO has published Quality Control Methods for Medicinal Plant Materials to support countries in developing national standards (5). In addition, an increasing number of national and regional pharmacopoeias include monographs on herbal materials.

Some common examples of problems involved with nomenclature of herbal medicines were presented by the Uppsala Monitoring Centre during the meeting. Lack of correct identification of herbal medicines was targeted as a common pharmacovigilance problem, so that the botanical verification and identification of herbal medicines was seen as a fundamental step towards ensuring safety.

Each plant should be identified according to the Latin binominal name. As an example, nomenclature problems can be illustrated by the confusion centred around the name Ginkgo biloba. Although there is only one species of Ginkgo, there are several synonymous names (Pterophyllus, Salisburia) and many common names. Furthermore, the leaves contain various flavonoid glycosides and the seeds contain various alkaloids, so that differentiation between leaves and seeds is very important. Ingredients are detailed in the Uppsala Monitoring Centre database as “Ginkgo leaves extract” but, depending on the method of extraction, different active ingredients will be obtained. Certain other related products are also described as Ginkgo biloba in the Uppsala Monitoring Centre data base. In addition, there is also Ginkor which comprises a mixture of ginkgo and troxerutin. Ginkor proto contains three ingredients, as does Friggs ginkgo Aristolochia. Although there are about 500 species, the Uppsala Monitoring Centre data base has only one report entry.

Following the presentations, a working group was convened which proposed that the definition of herbal medicines, for the purposes of pharmacovigilance, should be extended to include "labelled and unlabelled plants and traditional medicines from animal and mineral origin" as set out in the WHO Guidelines for the Assessment of Herbal Medicines (2). Discussion also took place on evaluation of herbal products based on safety quality and efficacy, registration and regulation adapted to the needs of individual countries, and development of reliable sources of information.

In monitoring the safety and efficacy of herbal medicines, education and communication are very important and the respective roles of the Uppsala Monitoring Centre and WHO in achieving this were emphasized.

The following recommendations were also made by the working group:

- A monitoring and surveillance system for herbal medicines should be developed in each country.
- Basic information should be made available to all countries, and access improved to international data bases.
- Pharmacovigilance activities should be strengthened between the WHO Programme on Traditional Medicines and the Uppsala Monitoring Centre.
- Adverse drug reaction reporting forms for herbal medicines should be in a similar format as those currently used for pharmaceuticals.
- Education of health professionals on the rational use of herbal medicines should be carried out by qualified herbalists.
• Public information and educational tools for consumers should be developed.

• Collaboration with poison control centres should be established.

• Health authorities should promote the development of pharmacognosy.

These recommendations will be implemented by the WHO Traditional Medicines Programme in collaboration with other partners in the WHO International Drug Monitoring Programme, and progress will be reported at the next Annual meeting of National Centres in November 2001.

References


Publications and Sources of Information

Bridging the digital divide
Public and private partners have teamed up to facilitate the flow of health information via the Internet. Major awards for electronic communication in science have been approved for four centres in Africa and five centres in central Asia and eastern Europe. This is the first phase of a public/private initiative — the Health Internetwork project — which aims to boost access by researchers and health workers to reliable information via the Internet and to improve global public health by facilitating the flow of information worldwide.

Partners in the initiative include the World Health Organization (WHO) and other UN organizations, the Open Society Institute (OSI), which is part of the Soros Foundation network, leading information providers ISI(r) and Silver Platter, and other public and private partners, possibly including the leading scientific publisher Elsevier.

In the first phase of the study, the nine centres are to be provided with a 'connectivity package' consisting of hardware, wide band connectivity, full access to several databases and more than 100 medical journals (online, full text). For their part, the centres will help work out how to introduce locally-produced information to the Internet, stressing priority public health programmes and local translation and adaptation of content as necessary. They will also decide how to expand the project to the rest of their country and region, and evaluate its impact.

Research, and the sharing of knowledge through research, is fundamental to improving public health. Through the Health Internetwork project, researchers and scientists will begin to read the same journals, search the same databases, join in the same discussion groups, compete for the same grants and it will bring them into the international community of researchers and eventually improve the dissemination of their own results. The project aims to facilitate research in countries that have first-hand experience of diseases and health issues that affect the poor.

After a one-year pilot phase, the intention is to extend the facility to a large number of needy countries. It is anticipated that, by the end of 2003, some 13 000 new health information access points in some 40 countries will be equipped with Internet technology, thus enabling communication and networking among public health information users, and improving monitoring of health situations.


India publishes ethical guidelines for biomedical research
The Indian Council of Medical Research has issued ethical guidelines for biomedical research on human subjects. The foreword sets the tone of the guidelines by drawing attention to the exciting and awesome breakthroughs in science being witnessed and the sense of urgency to address critical issues such as biotechnology. It warns that the ability of scientists and society to handle the forces of change will be crucial to future management of biomedical research and to the possibilities offered to society. As in all frontiers of research, this new knowledge will raise delicate and sometimes difficult issues of human values.

Following the statements of general principles, the guidelines go on to give detailed rules on ethical review procedures, general ethical issues, and specific principles for clinical evaluation of drugs, vaccines, devices, diagnostics and herbal remedies. Also included are sections on human genetics research, transplantation, use of foetal tissue, and assisted reproductive technologies.

Ethical Guidelines for Biomedical Research on Human Subjects is available from: Indian Council of Medical Research, Vigan Bhawan Annexe, Maulana Azad Road, New Delhi 110011, India.
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—73) and Recommended (1—35) International Nonproprietary Names can be found in Cumulative List No. 9, 1996. 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—73) et recommandées (1—35) dans la Liste récapitulative No. 9, 1996. 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—73) y Recomendadas (1—35) se encuentran reunidas en Cumulative List No. 9, 1996. 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 íntimamente 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 84

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 84 Proposed INN not later than 31 July 2001.

Dénominations communes internationales proposées: Liste 84

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 84 de DCI Proposées le 31 de juillet 2001 au plus tard.

Denominaciones Comunes Internacionales Propuestas: Lista 84

Cualquier persona puede dirigir observaciones o 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 84 de DCI Propuestas el 31 de julio de 2001 a más tardar.

<table>
<thead>
<tr>
<th>Proposed INN (Latin, English, French, Spanish)</th>
<th>Chemical name or description: Action and use: Molecular formula</th>
<th>Chemical Abstracts Service (CAS) registry number: Graphic formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>abrineurinum (abrineurin)</td>
<td>N-\text{-}L\text{-}methionylneurotrophic factor (human brain-derived) cyclic ((13\rightarrow80),(58\rightarrow109),(68\rightarrow111)\text{-}tris\text{-}disulfide), dimer \textit{neurotrophic factor}</td>
<td>\text{C}<em>{587}\text{H}</em>{947}\text{N}<em>{177}\text{O}</em>{177}\text{S}_{10} \text{ (monomer) 178535-93-8}</td>
</tr>
<tr>
<td>abrineurine</td>
<td>\text{d}ime\text{r}e \text{du} ((13\rightarrow80),(58\rightarrow109),(68\rightarrow111)\text{-}tris\text{-}disulfure) cyclique du \text{\textit{L}}\text{-}méthionylfacteur neurotrophique \text{cé}rébral \text{humain} \textit{facteur de croissance neuronal}</td>
<td></td>
</tr>
<tr>
<td>abrineurina</td>
<td>\text{d}ím\text{e}r\text{o} \text{d}el ((13\rightarrow80),(58\rightarrow109),(68\rightarrow111)\text{-}tris\text{-}disulfuro)c\text{íc}lic\text{o} \text{d}el \text{facteur} \text{N}\text{-}L\text{-}metionilneurotrófico \text{ (derivado de cerebro humano)} \textit{factor de crecimiento neuronal}</td>
<td></td>
</tr>
</tbody>
</table>

$$\text{HSDPARRGEL SVCDISEWV TAADKTAVD MSGGTVTVLE}$$

$$\text{KVPVSKGQLK QYFYTEKCPN MGYTEKCRG IDKRHWNSQC}$$

$$\text{RTTQSYVRAL TMDSKKRIGW RFIRIDTSCV CTLTIKRGR}$$
**acidum carglumicum**
carglumic acid  
*N*-carbamoyl-L-glutamic acid  
*antihiperamonaemia agent*

**acidum lidadronicum**
lidadronic acid  
[1-amino-3-(dimethylamino)propyldiene]diphosphonic acid  
*carrier*

**agalsidasum alfa**
agalsidase alfa  
human alpha-galactosidase isoenzyme A, isolated from human cell line, clone RAG 001, glycoform α  
*enzyme*
Proposed INN: List 84

**agalsidase beta**

\[ C_{2029}H_{3080}N_{544}O_{587}S_{27} \]

(subunit protein moiety reduced)

\[ \text{LDNGLARTPT MgwLHWERFM CNLDCQEEPQ SCISEKLFME} \]
\[ \text{MAELMVESEG WDAQYELICD DDCEMPQRD SEGRLOQAPQ} \]
\[ \text{RFPHGIRQLA NYVHSKGLKL GIYADVNGKT CAGFGPSGQI} \]
\[ \text{YDIDAQTFAD WGVDLKFDG CYCDSLENLA DGYKHMSLAL} \]
\[ \text{NRTGRSIVYS CEWPLYMWPQ QKPNYITEEIQ YCNHWRNFAD} \]
\[ \text{IDDSWKSIKS ILDWTSPNQG RIVDVGAPGG WNDPDMVLIG} \]
\[ \text{NFGLSNQNQV TQMALWAIMA APLFSNDLHR HISPQAKALL} \]
\[ \text{QDKVIPAVIME DPLGKQGYQQL RQCDNFEVWE RPLSGLAV} \]
\[ \text{AMINRQIEIGG PLYTIAVAS LGKVACNPA CFITQLPQVK} \]
\[ \text{RKLGFYEWTS RLRSHINPTG AVLQLLENTM QMSLKD} \]

* glycosylation sites (asparagine)
* sites de glycosylation (asparagine)
* posiciones de glicosilación (asparagine)

\[ 104138-64-9 \] (for protein moiety)

**agalsidase beta**

\[ C_{2029}H_{3080}N_{544}O_{587}S_{27} \]

(subunit protein moiety reduced)

\[ \text{LDNGLARTPT MgwLHWERFM CNLDCQEEPQ SCISEKLFME} \]
\[ \text{MAELMVESEG WDAQYELICD DDCEMPQRD SEGRLOQAPQ} \]
\[ \text{RFPHGIRQLA NYVHSKGLKL GIYADVNGKT CAGFGPSGQI} \]
\[ \text{YDIDAQTFAD WGVDLKFDG CYCDSLENLA DGYKHMSLAL} \]
\[ \text{NRTGRSIVYS CEWPLYMWPQ QKPNYITEEIQ YCNHWRNFAD} \]
\[ \text{IDDSWKSIKS ILDWTSPNQG RIVDVGAPGG WNDPDMVLIG} \]
\[ \text{NFGLSNQNQV TQMALWAIMA APLFSNDLHR HISPQAKALL} \]
\[ \text{QDKVIPAVIME DPLGKQGYQQL RQCDNFEVWE RPLSGLAV} \]
\[ \text{AMINRQIEIGG PLYTIAVAS LGKVACNPA CFITQLPQVK} \]
\[ \text{RKLGFYEWTS RLRSHINPTG AVLQLLENTM QMSLKD} \]

\[ 104138-64-9 \] (for protein moiety)
**alefaceptum**

**alefacept**

1-92-antigen LFA-3 (human) fusion protein with human immunoglobulin G1 (hinge-C$_{103}$-C$_{103}$ $\gamma$1-chain), dimer

*antipsoriatic*

**aléfacept**

diamètre de la protéine de fusion entre le 1-92-LFA-3 humain et la région charnière C$_{103}$-C$_{103}$ de la chaîne $\gamma$1 de l'immunoglobuline G1 humaine

*antipsoriasique*

**alefacept**

dímero de la proteína de fusión entre el 1-92-antígeno LFA-3 humano y la immunoglobulina G1 (cadena $\gamma$1 bisagra-C$_{103}$-C$_{103}$)

*antipsoriásico*

$$C_{326}H_{500}N_{840}O_{988}S_{20}$$ 222535-22-0

FSQQIYGVVY GNVTFHPSN VPLKEVLWKK QDKVAELEN
SEFRAFSSFK NRVYLDTVSG SLTIYNLTSS DEDEYEMESP
NIIDTMKFFL YVDKHTTCPP CPAPELLGGP SVFLFPPPKPK
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK
TKPREEQYNS TYRVSVLTVA LHQDWLNGKE YKCKVSNKAL
PAPIEKTIASK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL
VKGFYPSSIDAK VEWESNGQPE NNYKTTPPVL DSDGSFFLYS
KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLPGK

**alfatradiolum**

**alfatradiol**

estra-1,3,5(10)-triene-3,17$\alpha$-diol

*topical*

**alfatradiol**

estra-1,3,5(10)-triène-3,17$\alpha$-diol

*topique inhibiteur de la 5$\alpha$-réductase*

**alfatradiol**

estra-1,3,5(10)-trieno-3,17$\alpha$-diol

*inhibidor tópico de la 5$\alpha$-reductasa*

$$C_{18}H_{25}O_2$$ 57-91-0
aprepitantum

aprepitant

3-\{(2R,3S)-3-(p-fluorophenyl)-2-\{[(\alpha R)-\alpha-methyl-3,5-bis(trifluoromethyl)benzyl]oxy\}[morpholinomethyl]-\Delta^3-1,2,4-triazolin-5-one

antiemetic, tachykinin receptor antagonist

aprépitant

5-\{(2R,3S)-2-\{(1R)-1-[3,5-bis(trifluorométhyl)phényléthoxy]-3-(4-fluorophényl)morpholin-4-il]méthyl\}-1,2-dihydro-3H-1,2,4-triazol-3-one

antiémétique, antagoniste des récepteurs de la tachykinine

aprepitant

5-\{(2R,3S)-2-\{(1R)-1-[3,5-bis(trifluorometil)fenil]etoxi]-3-(4-fluorofenil)morfolin-4-il]metil\}-1,2-dihidro-3H-1,2,4-triazol-3-ona

antiemético, antagonista del receptor de taquiquinina

C_{23}H_{21}F_{7}N_{4}O_{3}

170729-80-3

aviscuminum

aviscumine
toxin ML-I (mistletoe lectin I) (Viscum album)

antineoplastic

aviscumine
toxine ML-I (lectine I de gui) (Viscum album) obtenue par génie génétique, constituée par deux chaînes peptidiques A (250 amino-acides) et B (264 amino-acides) liées entre elles par un pont disulfure

antineoplásico

aviscumina
toxina ML-I (lectina I de muérdago) (Viscum album) obtenida por ingeniaria genética, constituida por dos cadenas peptídicas A (250 aminoácidos) y B (264 aminoácidos) unidas entre sí por un puente disulfuro
balaglitazonum
balaglitazone

\((\pm)-5\)-(p-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinyl)methoxy]benzyl)-2,4-thiazolidinedione

antidiabetic

balaglitazone

\((5RS)-5\)-[4-[(3-méthyl-4-oxo-3,4-dihydroquinazolin-2-y]-thiazolidine-2,4-dione

antidiabétique

balaglitazona

\((\pm)-5\)-[p-[(3,4-dihidro-3-metil-4-oxo-2-quinazolinil)metoxi]bencil]-2,4-tiazolidinadiona

antidiabético

\[C_{20}H_{17}N_{3}O_{4}S\] 199113-98-9
bimosiamosum

bimosiamose  
[hexane-1,6-diylbis[6'-((α-D-mannopyranosyloxy)phenyl-3',3-diyl)]diacetic acid  
non-steroid anti-inflammatory

bimosiamose  
acide [hexane-1,6-diylbis[6'-((α-D-mannopyranosyloxy)phenyl-3',3-diyl)]diacétique  
anti-inflammatoire non stéroïden

bimosiamosa  
ácido [hexano-1,6-diilbis[6'-(α-D-manopiranosiloxy)bifenil-3',3-diil]]diacético  
antiinflamatorio no esteroideo

\[ C_{46}H_{54}O_{16} \] 187269-40-5

brostallicinum

brostallicin  
4-(2-bromoacrylamido)-N''''-(2-guanidinoethyl)-1',1'',1''''-tetramethyl-N,4',4'',N'',4''''-quater[pyrrole-2-carboxamide]  
antineoplastic

brostallicine  
antinéoplasique

brostalicina  
4-(2-bromoacrilamido)-N''''-(2-guanidinoetil)-1',1'',1''''-tetrametil-N,4',4'',N'',4''''-cuater[pirrol-2-carboxamida]  
antineoplásico

\[ C_{30}H_{35}BrN_{12}O_{5} \] 203258-60-0
**dilomotecanum**

*dilomotecan*  
\((5R)-5\text{-}\text{ethyl-9,10-difluoro-1,4,5,13-tetrahydro-5-hydroxy-3H,15H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione}^{\text{antineoplastic}}\)

**dilomotécan**  
\((5R)-5\text{-éthyl-9,10-difluoro-5-hydroxy-1,4,5,13-tétrahydro-3H,15H-oxépino[3',4':6,7]indolizino[1,2-b]quinoléine-3,15-dione}^{\text{antineoplasique}}\)

**dilomotecán**  
\((5R)-5\text{-etil-9,10-difluoro-1,4,5,13-tetrahidro-5-hidroxi-3H,15H-oxepino[3',4':6,7]indolizino[1,2-b]quinolina-3,15-diona}^{\text{antineoplásico}}\)

\[
\text{C}_{21}\text{H}_{16}\text{F}_{2}\text{N}_{2}\text{O}_{4} \quad 220997-97-7
\]

**edotreotide**

*N\text{-}[[4,7,10}\text{-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl}][\text{acetil}]-D-\text{-fenilalanil-L-cysteinyll-L-tyrosil-D-trytophil-L-lysyl-L-threonyl-N'\text{-}[1R,2R]-2-hidroxy-1-(hidroxymetil)propily-L-cystéinamidade}^{\text{antineoplastic}}\) cyclic \((2\rightarrow7)\)-disulfide

\[
\text{(2→7)-disulfure cyclique du [N\text{-}[4,7,10}\text{-tris(carboxyméthyl)-1,4,7,10-tétraazacyclododéc-1-yl}][\text{acétyl}]-D\text{-phénylalanil-L-cystéinyll-L-tyrosyl-D-trytophyll-L-lysyl-L-thréonyl-N'\text{-}[1R,2R]-2-hidroxy-1-(hidroxyméthyl)propily-L-cystéinamidade}^{\text{antineoplasique}}\)
\]

\[
\text{C}_{65}\text{H}_{92}\text{N}_{14}\text{O}_{18}\text{S}_{2} \quad 204318-14-9
\]
edronocainum  
edronocaine  
\[N,1\text{-dimethyl-2'-}(m\text{-propoxyphenoxy})\text{diethylamine}\]  
\textit{analgesic, sodium channel blocker}\n
édronocaïne  
\[N\text{-méthyl-}N\text{-}[2\text{-}(3\text{-propoxyphén oxy})\text{éthyl}]\text{propan-2-amine}\]  
\textit{analgésique, antagoniste des canaux sodiques}\n
edronocaina  
\[N,1\text{-dimetil-2'-}(m\text{-propoxifenoxi})\text{dietilamina}\]  
\textit{analgésico, bloqueador de los canales del sodio}\n
C_{15}H_{25}NO_2  
190258-12-9

---

eflucimibum  
eflucimibe  
\[(S)-2\text{-}(dodecylthio)-4\text{'-hydroxy-}2',3',5'\text{-trimethyl-2-phenylacetanilide}\]  
\textit{antihyperlipidaemic}\n
éflucimibe  
\[(2S)-2\text{-}(dodécylsulfanyl)-N\text{-}(4\text{-hydroxy-}2,3,5\text{-triméthylphényl})\text{-}2\text{-phénylacétamide}\]  
\textit{antihyperlipidémiant}\n
eflucimiba  
\[(S)-2\text{-}(dodeciltio)-4\text{'-hidroxi-}2',3',5'\text{-trimetil-2-fenilacetanilida}\]  
\textit{antihiperlipémico}\n
C_{29}H_{43}NO_2S  
202340-45-2

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eganoprostum  
eganoprost  
methyl \[(Z)-7\text{-}[\{1R,2R,3R\}\text{-}2\text{-}[\{1E,3S,7R\}\text{-}3,7\text{-dihydroxy-1-octeny l}\text{-}3\text{-hydroxy-5-oxocyclopentyl}\text{-}5\text{-heptenoate}\]  
\textit{prostaglandin}\n
éganoprost  
\[(Z)-7\text{-}[\{1R,2R,3R\}\text{-}2\text{-}[\{1E,3S,7R\}\text{-}3,7\text{-dihydroxyoct-1-ényl}\text{-}3\text{-hydroxy-5-oxocyclopentyl}\text{-}hept-5-énoate de méthyle}\]  
\textit{prostaglandine}\n
eganoprost  
\[(Z)-7\text{-}[\{1R,2R,3R\}\text{-}2\text{-}[\{1E,3S,7R\}\text{-}3,7\text{-dihidroxioc-t-1-enil}\text{-}3\text{-hidroxi-5-oxociclopentil}\text{-}hept-5-enoato de metilo}\]  
\textit{prostaglandina}
emodepsidum
cemodepside
cyclo[(R)-lactoyl-N-methyl-L-leucyl-(R)-3-(p-morpholinophenyl)lactoyl-
N-methyl-L-leucyl-(R)-lactoyl-N-methyl-L-leucyl-(R)-3-
(p-morpholinophenyl)lactoyl-N-methyl-L-leucyl]
ampelminthic

temodepside
cyclo[(R)-2-hydroxypropanoyl-(N-methyl-L-leucyl)-[(R)-3-[4-(morpholin-
4-yl)phényl]-2-hydroxypropanoyl]-(N-méthyl-L-leucyl)]
ampelminthique

temodepsida
ciclo[(R)-lactoil-N-metil-L-leucil-(R)-3-(p-morfolinofenil)lactoil-N-metil-L-leucil-
(R)-lactoil-N-metil-L-leucil-(R)-3-(p-morfolinofenil)lactoil-N-metil-L-leucil]
antihelmínico

erlizumabum
erlizumab
immunoglobulin G1, anti-(human antigen CD18) (human-mouse monoclonal
F(ab')₂ fragment γ1-chain), disulfide with human-mouse monoclonal light
chain, dimer
immunomodulator

erlizumab
immunoglobuline G1, anti-(antigène CD18 humain) fragment F(ab')₂
(chaîne γ1 de l’anticorps monoclonal de souris humanisé), dimère du
disulfure avec la chaîne légère de l’anticorps monoclonal de souris humanisé
immunomodulateur

erlizumab
immunoglobulina G1, anti-(antígeno CD18 humano) fragmento F(ab')₂,
(cadena y1 del anticuerpo monoclonal humanizado de ratón), dímero del
disulfuro con la cadena ligera del anticuerpo monoclonal humanizado de
ratón
immunomodulador
ertapenem
ertapenem
ertapenem

(4R,5S,6S)-3-[(3S,5S)-5-[(3-carboxyphenyl)carbamoyl]-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

acide (4R,5S,6S)-3-[(3S,5S)-5-[(3-carboxyphényl)carbamoyl]pyrrolidin-3-yl]sulfanyl]-6-[(1R)-1-hydroxyéthyl]-4-méthyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ène-2-carboxylique

acido (4R,5S,6S)-3-[(3S,5S)-5-[(3-carboxifenil)carbamoil]pirrolidin-3-il]sulfanil]-6-[(1R)-1-hidroxetil]-4-metil-7-oxo-1-azabiciclo[3.2.0]hept-2-eno-2-carboxilico

\[C_{22}H_{25}N_{3}O_{7}S\] 153832-46-3

etoricoxib
etoricoxib
etoricoxib

5-chloro-6'-methyl-3-[p-(methylsulfonyl)phenyl]-2,3'-bipyridine
cyclooxygenase-2 inhibitor

5-chloro-6'-méthyl-3-[4-(méthylsulfonil)phényl]-2,3'-bipyridyle
inhibiteur de la cyclooxygénase-2

5-cloro-6'-metil-3-[4-(metilsulfonil)fenil]-2,3'-bipiridilo
inhibidor de la cicloxigenasa-2

\[C_{18}H_{15}ClN_{2}O_{2}S\] 202409-33-4
**eufauserasum**

**eufauserase**  
broad spectrum serine-protease enzyme, extracted from the Antarctic krill (*Euphausia superba*) enzyme

**eufausérase**  
protéase à large spectre (enzyme à sérine) extraite de krill de l'Antarctique (*Euphausia superba*) enzyme

**eufauserasa**  
serin-proteasa de amplio espectro extraida del camarón antártico (*Euphausia superba*) enzima

\[ \text{C}_{1170}\text{H}_{1764}\text{N}_{300}\text{O}_{387}\text{S}_{14} \]

**farglitazarum**

**farglitazar**  
\[ N-(\text{o-benzoylphenyl})-\text{O}-(2-(\text{5-methyl-2-phenyl-4-oxazolyl})\text{ethyl})-\text{L-tyrosine} \]

**farglitazar**  
acid (2S)-2-[(2-benzoylphényl)amino]-3-[4-[2-(5-méthyl-2-phényloxazol-4-yl)éthoxy]phényl]propanoïque

**farglitazar**  
ácido (2S)-2-[(2-benzoifenil)amino]-3-[4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil]propanoico

\[ \text{C}_{34}\text{H}_{30}\text{N}_{2}\text{O}_{5} \]

196808-45-4
**fesoterodinum**  
**fesoterodine**  
2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate  
treatment of urinary incontinence

**fésotérôdine**  
2-méthylpropanoate de 2-[(1R)-3-[bis(1-méthyléthyl)amino]-1-phénylpropyl]-4-(hydroxyméthyl)phényle  
traitement de l’énurésie

**fesoterodina**  
2-metilpropanoato de 2-[(1R)-3-[bis(1-metiletil)amino]-1-fenilpropil]-4-(hidroximetil)fenilo  
tratamiento de la incontinencia urinaria

C_{26}H_{37}NO_{3} 286930-03-8

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**gavilimomabum**  
**gavilimomab**  
immunoglobulin M, anti-(human antigen CD147) (mouse monoclonal ABX-CBL \( \mu \)-chain), disulfide with mouse monoclonal ABX-CBL light chain, pentamer  
immunomodulator

**gavilimomab**  
immunoglobuline M, anti-(antigène CD147 humain) (chaîne \( \mu \) de l’anticorps monoclonal de souris ABX-CBL), pentamère du disulfure avec la chaîne légère de l’anticorps monoclonal de souris ABX-CBL  
immunomodulateur

**gavilimomab**  
immunoglobulina M, anti-(antígeno CD147 humano) (cadena \( \mu \) del anticuerpo monoclonal de ratón ABX-CBL), pentámero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón ABX-CBL  
immunomodulador

244096-20-6

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**gemopatrilatum**  
**gemopatrilat**  
\((6S)-\text{hexahydro-6-}[(\alpha,S)-\text{mercaptohydrocinnamido}]\,-2,2\text{-dimethyl-7-oxo-} \text{1H-azepine-1-acetic acid}

angiotensin-converting enzyme inhibitor, endopeptidase inhibitor

**gémopatilate**  
acide \([(6S)-2,2\text{-diméthyl-7-oxo-}6-][[(2S)-3\text{-phényl-}2\text{-sulfanylpropanoyl}] \text{amino}]\text{hexahydro-1H-azépin-1-yl} \text{acétique}

inhibiteur de l’enzyme de conversion de l’angiotensine, inhibiteur de l’endopeptidase
**gemopatrilat**

ácido [(6S)-2,2-dimetil-7-oxo-6-[[2S]-3-fenil-2-sulfanilpropano][amino]hexahidro-1H-azepin-1-il]acético

inhibidor de la enzima conversora de la angiotensina, inhibidor de la endopeptidasa

\[
C_{19}H_{26}N_{2}O_{4}S \quad 160135-92-2
\]

![Structure of gemopatrilat](image)

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**imatinibum**

imatinib

\(\alpha\)-(4-metil-1-piperazinil)-3’-[[4-(3-piridil)-2-pirimidinil]amino]-p-tolu-p-toluidide

antineoplásico

\[
C_{29}H_{31}N_{7}O \quad 152459-95-5
\]

![Structure of imatinib](image)

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**insulinum glulisinum**

insulin glulisine

\[3^B-L-lysine,29^B-L-glutamic acid\]insulin (human)

antidiabético

\[
C_{258}H_{384}N_{64}O_{78}S_{6} \quad 207748-29-6
\]

![Structure of insulin glulisine](image)
**lemalesomabum**

Immunoglobulin G1, anti-(human NCA-90 granulocyte cell antigen) (mouse monoclonal IMMU-MN3 \( \gamma 1 \)-chain), disulfide with mouse monoclonal IMMU-MN3 \( \kappa \)-chain, dimer

**lémalésomab**

Immunoglobuline G1, anti-(antigène cellulaire du granulocyte humain NCA-90) (chaîne \( \gamma 1 \) de l’anticorps monoclonal de souris IMMU-MN3), dimère du disulfure avec la chaîne \( \kappa \) de l’anticorps monoclonal de souris IMMU-MN3

**lemalesomab**

Immunoglobulina G1, anti-(antígeno celular del granulocito humano NCA-90) (cadena \( \gamma 1 \) del anticuerpo monoclonal de ratón MMU-MN3), dímero del disulfuro con la cadena \( \kappa \) del anticuerpo monoclonal de ratón MMU-MN3

250242-54-7

**litomeglovirum**

Aminoacétate de 3-[[4-[[5-(diméthylamino)naptalén-1-yl]sulfónyl]amino]phényl]amino]-2,2-diméthyl-3-oxopropyle

Antiviral

\[ C_{25}H_{30}N_4O_5S \]

321915-31-5

**micafunginum**

(4\( R \),5\( R \))-4,5-dihydroxy-\( N^2-\)([4-[(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-l-ornithyl-l-threonyl-trans-4-hydroxy-l-prolyl-(4\( S \))-4-hydroxy-4-[4-hydroxy-3-(sulfoxy)phenyl]-l-threonyl-(3\( R \))-3-hydroxy-l-glutaminyl-(3\( S \),4\( S \))-3-hydroxy-4-méthyl-l-proline cyclic (6→1)-peptide

Antifungal
micafungina


antifúngico

C_{56}H_{71}N_{9}O_{23}S

mozenavirum

mozenavir

(4R,5S,6S,7R)-1,3-bis(3-aminobenzyl)-4,7-dibenzylhexahydro-5,6-dihidroxy-2H-1,3-diazepin-2-one

antiviral

mozenavir

(4R,5S,6S,7R)-1,3-bis(3-aminobenzyl)-4,7-dibenzyl-5,6-dihidroxyhexahydro-2H-1,3-diazepin-2-one

antiviral

mozenavir

(4R,5S,6S,7R)-1,3-bis(3-aminobencil)-4,7-dibencil-5,6-dihidroxihexahidro-2H-1,3-diazepin-2-ona

antiviral

C_{33}H_{36}N_{4}O_{3}

174391-92-5
**navuridinum**

**navuridine**

3'-azido-2',3'-dideoxyuridine

*antiviral*

**navuridine**

1-(3-azido-2,3-didésoxy-β-érythro-pentofuranosyl)pyrimidine-2,4(1H,3H)-dione

*antiviral*

**navuridina**

3'-azido-2',3'-didesoxiuridina

*antiviral*

C₉H₁₁N₅O₄ 84472-85-5

![Chemical structure of navuridinum](image)

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**neramexanum**

**neramexane**

1,3,3,5,5-pentamethylcyclohexylamine

*NMDA receptor antagonist*

**néramexane**

1,3,3,5,5-pentaméthylcyclohexanamine

*antagoniste des récepteurs du NMDA*

**neramexano**

1,3,3,5,5-pentametilciclohexilamina

*antagonista de los receptores del NMDA*

C₁₁H₂₃N 219810-59-0

![Chemical structure of neramexanum](image)

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**nolomirolum**

**nolomirole**

(±)-5,6,7,8-tetrahydro-6-(methylamino)-1,2-naphthylene diisobutyrate

*dopamine receptor agonist*

**nolomirole bis(2-méthylpropanoate) de (6RS)-6-(méthylamino)-5,6,7,8-tétrahyronaphtaléne-1,2-diyle**

*agoniste des récepteurs de la dopamine*

**nolomirol**

diisobutirato de (±)-5,6,7,8-tetrahidro-6-(metilamino)-1,2-naftileno

*agonista de los receptores de la dopamina*
omaciclovirum

omaciclovir

9-[(R)-4-hydroxy-2-(hydroxymethyl)butyl]guanine
antiviral

omaciclovir

2-amino-9-[(2R)-4-hydroxy-2-(hydroxymethyl)butyl]-1,9-dihydro-6H-purin-6-one
antiviral

omaciclovir

9-[(R)-4-hidroxi-2-(hidroximetil)butil]guanina
antiviral

omalizumabum

omalizumab

immunomodulator

omalizumab

immunoglobuline G, anti-(région Fc de l’immunoglobuline E humaine) (chaîne γ de l’anticorps monoclonal de souris E25 clone pSVIE26 humanisé), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal de souris E25 clone pSVIE26 humanisé
immunomodulateur

omalizumab

immunoglobulina G, anti-(región Fc de la immunoglobulina E humana) (cadena γ del anticuerpo monoclonal humanizado de ratón E25 clon pSVIE26), dímero del disulfuro con la cadena κ del anticuerpo monoclonal humanizado de ratón E25 clon pSVIE26
immunomodulador
peginterferonum alfa-2a

mono(\textsuperscript{N},\textsuperscript{N}-dicarboxy-L-lysyl)interferon alfa-2a, diesters with polyethylene glycol monomethyl ether

The molecular mass of the pegylated part may be indicated in the name by adding a number, for example: peginterferon alfa-2a (40KD).

*immunomodulator*

peginterféron alfa-2a

interféron alfa-2a dont une des lysines en position 31, 121, 131 ou 134 est acylée par le \textsuperscript{N},\textsuperscript{N}-bis[méthylpoly(oxyéthylène)oxycarbonyl]-L-lysyl

La masse molaire de la partie polyéthyléneglycol peut être indiquée dans la DCI, par exemple: peginterféricron alfa-2a (40KD).

*immunomodulateur*

peginterferón alfa-2a

diésteres del mono (\textsuperscript{N},\textsuperscript{N}-dicarboxi-L-lisil) interferón alfa-2a, con polietilenglicolmonomethyl éter

La masa molecular de la parte pegilada, si es necesario, puede indicarse en el nombre añadiendo un número, por ejemplo: peginterferón alfa-2a (40KD).

*inmunomodulador*

198153-51-4

peginterferonum alfa-2b

monocarboxyinterferon alfa-2b, diesters with polyethylene glycol monomethyl ether

The molecular mass of the pegylated part may be indicated in the name by adding a number, for example: peginterferon alfa-2b (12KD).

*immunomodulator*

peginterféron alfa-2b

interféron alfa 2b dont un azote de la cystéine 1 ou d’une lysine 31, 121 ou 134 est engagé dans une liaison carbamate avec l’éther monométhylène glycol

La masse molaire de la partie polyéthyléneglycol peut être indiquée dans la DCI, par exemple: peginterféricron alfa-2b (12KD).

*immunomodulateur*
peginterferón alfa-2b
diésteres del monocarboxiinterferón alfa-2b con éter monometílico de polietilenglicol
La masa molecular de la parte pegilada, si es necesario, puede indicarse en el nombre añadiendo un número, por ejemplo: peginterferón alfa-2b (12KD).
inmunomodulador

215647-85-1

215647-85-1

pipendoxifenum
pipendoxifene 2-(p-hydroxyfenil)-3-metil-1-[p-(2-piperidinoethoxy)benzil]indol-5-ol antineoplástico

pipendoxifène 2-(4-hydroxyphényl)-3-âméthyl-1-[4-[2-(pipéridin-1-yl)éthoxy]benzyl]-1H-indol-5-ol antinéoplasique

pipendoxifeno
2-(4-hidroxifenil)-3-metil-1-[4-[2-(piperidin-1-il)etoxi]bencil]-1H-indol-5-ol antineoplásico

C_{29}H_{32}N_{2}O_{3} 198480-55-6

pitrrakinraum
pitrrakinra  L-methionyl-[121-aspartic acid,124-aspartic acid]interleukin-4 immunomodulator, interleukin-4 receptor antagonist

pitrrakinra  L-méthionyl-[121-acide aspartique,124-acide aspartique]interleukine-4 immunomodulateur, antagoniste des récepteurs de l’interleukine-4

pitrrakinra  L-metionil-[121-ácido aspártico,124-ácido aspártico]interleucina-4 immunomodulador, antagonista del receptor de la interleukina-4
pradofloxacinum

pradofloxacin

8-cyano-1-cyclopropyl-6-fluoro-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid antibacterial

C_{655}H_{1054}N_{190}O_{200}S_8

HKCDITLQEI IKTLSNLTEQ KTLCTELTVT DIFAASKNTT
EKETFCRAAT VLRQFYSHHE KDTRCLGATA QOFHRHKQLI
RFLKRLDRLN WGLAGLNSCP VKEANQSTLE NFLERLKTIM
DEKDSKCSS

pradofloxacine

acide 8-cyano-1-cyclopropyl-6-fluoro-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoléine-3-carboxylique antibactérien

pradofloxacina

ácido 8-ciano-1-ciclopropil-6-fluoro-7-[(4aS,7aS)-octahidro-6H-pirrolo[3,4-b]piridin-6-il]-4-oxo-1,4-dihidroquinolina-3-carboxílico antibacteriano

reglitazarum

reglitazar

(4RS)-4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-3,5-isoxazolidinedione antidiabetic

C_{21}H_{21}FN_{4}O_{3} 195532-12-8

reglitazar

réglitazar

(4RS)-4-[4-[2-(5-méthyl-2-phényloxazol-4-yl)thoxy]benzyl]isoxazolidine-3,5-dione antidiaabétique

reglitazar

reglitazar (4RS)-4-[4-[2-(5-metil-2-feniloxazol-4-il)etoxi]bencil]isoxazolidina-3,5-diona antidiabético

C_{22}H_{20}N_{2}O_{5} 170861-63-9

and enantiomer et énantiomère y enantiómero
rivoglitazone

(±)-5-[(6-methoxy-1-methyl-2-benzimidazoly)methoxy]benzyl]-2,4-thiazolidinedione

antidiabetic

rivoglitazone

(5RS)-5-[4-[(6-méthoxy-1-méthyl-1H-benzimidazol-2-yl)méthoxy]=benzyl]thiazolidine-2,4-dione

antidiabétique

rivoglitazona

(5RS)-5-[4-[(6-metoxi-1-metil-1H-bencimidazol-2-il)metoxi]bencil]tiazolidina-2,4-diona

antidiabético

C_{20}H_{19}N_{3}O_{4}S

185428-18-6

sabiporidum

N-carbamimidoyl-4-[4-(1H-pyrrol-2-ylcarbonyl)piperazin-1-yl]-3-(trifluoromethyl)benzamide

Na^+/H^+ antiport inhibitor

sabiporide

N-carbamimidoyl-4-[4-(1H-pyrrol-2-ylcarbonyl)pipérazin-1-yl]-3-(trifluorométhyl)benzamide

inhibiteur de l'échange Na^+/H^+

sabiporida

N-carbamimidoil-4-[4-(1H-pirrol-2-ilcarbonil)pipazin-1-il]-3-(trifluorometil)benzamida

inhibidor del transporte activo Na^+/H^+

C_{18}H_{19}F_{3}N_{6}O_{2}

261505-80-0
safinamidum
safinamide
(+)-(S)-2-[[p-([m-fluorobenzyl]oxy)benzyl]amino]propionamide
anticonvulsant

safinamide
(2S)-2-[[4-(3-fluorobenzyloxy)benzyl]amino]propanamide
anticonvulsivant

safinamida
anticonvulsivo

C_{17}H_{19}FN_{2}O_{2} 133865-89-1

sibenadetum
sibenadet
dopamine receptor agonist/β-adrenoreceptor agonist

sibénadet
agoniste dopaminergique/adrénergique

sibenadet
agonista de los receptores de la dopamina/agonista de los receptores β-adrenérgicos

C_{22}H_{28}N_{2}O_{5}S_{2} 154189-40-9

soblidotinum
soblidotin
N^\{N,N\}-dimethyl-L-valyl-N^\{1S,2R\}-2-methoxy-4-[[2S]-2-[[1R,2R]-1-methoxy-2-methyl-3-oxo-3-[[2-phenylethyl]amino]propyl]-1-pyrrolidinyl]-1-[[1S]-1-methylpropyl]-4-oxobuty]-N^\{\}-methyl-L-valinamide
antineoplastic
soblidotine (2S)-2-[(2S)-2-(dimethylamino)-3-methylbutanoyl]amino]-N-[(1S,2R)-2-méthoxy-4-[(2S)-2-[(1R,2R)-1-méthoxy-2-méthyl-3-oxo-3-[(2-phenyléthyl]amino]propyl]pyrrolidin-1-yl]-1-{(1S)-1-méthylpropyl]-4-oxobutyl]-N,3-diméthylbutanamide

soblidotina (2S)-2-[(2S)-2-(dimetilamino)-3-metilbutanoil]amino]-N-[(1S,2R)-2-metoxi-4-[(2S)-2-[(1R,2R)-1-metoxi-2-metil-3-oxo-3-[(2-feniletil]amino]propil]=pirrrolidin-1-il]-1-{(1S)-1-metilpropil]-4-oxobutil]-N,3-dimetilbutanamida

\[
\text{C}_{39} \text{H}_{67} \text{N}_5 \text{O}_6, \quad 149606-27-9
\]

soneclosanum

soneclosan 5-chloro-2-(p-chlorophenoxy)phenol

antimicrobial

sonéclosan 5-chloro-2-(4-chlorophénoxy)phénol

antimicrobien

soneclosán 5-cloro-2-(p-clorofenoxi)fenol

antimicrobiano

\[
\text{C}_{12} \text{H}_8 \text{Cl}_2 \text{O}_2, \quad 3380-30-1
\]

sumanirolum

sumanirole (R)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5,1-ij]quinolin-2(1H)-one

antiparkinsonian, dopamine receptor agonist

sumanirole (5R)-5-(méthylamino)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoléin-2(1H)-one

antiparkinsonien, agoniste des récepteurs de la dopamine

sumanirol (5R)-5-(metilamino)-5,6-dihidro-4H-imidazo[4,5,1-ij]quionlín-2(1H)-ona

antiparkinsoniano, agonista de los receptores de la dopamina
taplitumomab paptoxum

**taplitumomab paptox**
immunoglobulin G1, anti-(human antigen CD19) (mouse monoclonal B43 γ1-chain), disulfide with mouse monoclonal B43 κ-chain, dimer, disulfide with protein PAP (pokeweed antiviral)
**immunomodulator**

**taplitumomab paptox**
immunoglobuline G1, anti-(antigène humain CD19) (chaîne γ1 de l'anticorps monoclonal de souris B43), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris B43, disulfure avec la protéine antivirale extraite du phytolaque (PAP)
**immunomodulateur**

**taplitumomab paptox**
immunoglobulina G1, anti-(antígeno humano CD19) (cadena γ1 del anticuerpo monoclonal de ratón B43), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón B43, disulfuro con la proteína PAP (proteína antiviral de Phytolacca americana)
**inmunomodulador**

235428-87-2

tezacitabimum

tezacitabine

**tezacitabine**
2'-deoxy-2'-(E)-fluoromethylene]cytidine
**antineoplastic**

tézacitabine
4-amino-1-[(2E)-2-(fluorométhyène)-2-désoxy-β-d-érythro-pentofuranosyl]pyrimidin-2(1H)-one
**antineoplasique**
tezacitabina
2'-desoxi-2'-(E)-fluorometileno]citidina
**antineoplásico**

C_{10}H_{12}FN_{5}O_{4}  130306-02-4
**tidembersatum**

*tidembersat*

\[N-(3\text{R},4\text{S})-6\text{-acetyl-3-hydroxy-2,2-dimethyl-4-chromanyl}-3,5\text{-difluorobenzamide}]

*antimigraine agent*

\[N-(3\text{R},4\text{S})-6\text{-acétyle-3-hydroxy-2,2-diméthyl-3,4-dihydro-2H-1-benzopyran-4-yl}-3,5\text{-difluorobenzamide}]

\[N-(3\text{R},4\text{S})-6\text{-acetil-3-hidroxi-2,2-dimetil-3,4-dihidro-2H-1-benzopiran-4-il}-3,5\text{-difluorobenzamida}]

*C_{20}H_{19}F_{2}NO_{4} 175013-73-7*

![Chemical structure of tidembersat]

**tilmacoxibum**

*tilmacoxib*

4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide

*cyclooxygenase-2 inhibitor*

4-(4-cyclohexyl-2-méthyl-5-oxazolyl-5-yl)-2-fluorobenzènesulfonamide

*inhibiteur de la cyclooxygénase-2*

4-(4-ciclohexil-2-metil-5-oxazoliil)-2-fluorobencenosulfonamida

*inhibidor de la cicloxigenasa-2*

*C_{16}H_{19}FN_{2}O_{3}S 180200-68-4*

![Chemical structure of tilmacoxib]

**tipifarnibum**

*tipifarnib*

(+)-6-[(R)-amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone

*antineoplastic*

(+)-6-[(R)-amino(4-chlorophényl)(1-méthyl-1H-imidazol-5-yl)méthyl]-4-(3-chlorophényl)-1-méthylquinoléin-2(1H)-one

*antinéoplasique*
tipifarnib

(+)-6-[(R)-amino(4-clorofenil)(1-metil-1H-imidazol-5-il)metil]-4-(3-clorofenil)-1-metilquinolina-2(1H)-ona
antineoplásico

C_{27}H_{22}Cl_{2}N_{4}O_192185-72-1

---

tomeglovirum
tomeglovir

\(N\-4-[[5-(dimethylamino)-1-naphthyl]sulfonyl]amino]phenyl\)-3-hydroxy-2,2-dimethylpropanamide
antiviral

C_{23}H_{27}N_{3}O_{4}S_233254-24-5

---

traxoprodilum
traxoprodil

\(1S,2S\)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenyl-1-piperaziny)propan-1-ol
NMDA receptor antagonist

--

traxoprodil

\(1S,2S\)-1-(4-hydroxyphényl)-2-(4-hydroxy-4-phénylpipérazin-1-yl)propan-1-ol
antagoniste des récepteurs du NMDA

--

traxoprodil

\(1S,2S\)-1-(4-hidroxifenil)-2-(4-hidroxi-4-fenilpiperazin-1-il)propan-1-ol
antagonista de los receptores del NMDA
tridolgosirum
tridolgosir (1S,2R,8R,8aR)-octahydro-1,2,8-indolizinetriol
antineoplastic

tridolgosir (1S,2R,8R,8aR)-octahydroindolizine-1,2,8-triol
antineoplasique

tridolgosir (1S,2R,8R,8aR)-octahidroindolizina-1,2,8-triol
antineoplásico

C_{20}H_{25}NO_{3} 134234-12-1

valomaciclovirum
valomaciclovir L-valine, 4-ester with 9-[(R)-4-hydroxy-2-(hydroxymethyl)butyl]guanine
antiviral

valomaciclovir (2S)-2-amino-3-méthylbutanoate de (3R)-3-[2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)méthyl]-4-hydroxybutyle
antiviral

valomaciclovir éster de L-valina con (3R)-3-[2-amino-1,6-dihidro-6-oxo-9H-purin-9-il)metil]-4-hidroxibutilo
antiviral

C_{15}H_{24}N_{6}O_{4}
vatalanibum
vatalanib
1-(p-chloroanilino)-4-(4-pyridylmethyl)phthalazine
antineoplastic

vatalanib
N-(4-chlorophenyl)-4-(pyridin-4-ylmethyl)phthalazin-1-amine
antineoplasique

vatalanib
1-(p-cloroanilino)-4-(4-piridilmetil)ftalazina
antineoplásico

C_{20}H_{15}ClN_{4} 212141-54-3

visilizumabum
visilizumab
immunoglobulin G2, anti-(human antigen CD3) (human-mouse monoclonal HuM291 y2-chain), disulfide with human-mouse monoclonal HuM291 k-chain, dimer
immunomodulator

visilizumab
immunoglobuline G2, anti-(antigène CD3 humain) (chaîne γ2 de l’anticorps monoclonal de souris HuM291 humanisé), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal de souris HuM291 humanisé
immunomodulateur

visilizumab
immunoglobulina G2, anti-(antígeno CD3 humano) (cadena γ2 del anticuerpo monoclonal humanizado de ratón HuM291), dímero del disulfuro con la cadena κ del anticuerpo monoclonal humanizado de ratón HuM291
immunomodulador

219716-33-3

ximelagatranum
ximelagatran
antithrombotic

ximélagatran
antithrombotique

ximelagatrán
antitrombotique
zelandopamum

zelandopam

(-)-(S)-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydro-7,8-isoquinolinediol

dopamine D1 receptor agonist

zélandopam

(-)-(4S)-4-(3,4-dihydroxyphényl)-1,2,3,4-tétrahydroisoquinoléine-7,8-diol

antagoniste des récepteurs de la dopamine D1

zelandopam

(-)-(S)-4-(3,4-dihidroxifenil)-1,2,3,4-tetrahydro-7,8-isoquinolinediol

antagonista de los receptores de la dopamina D1

C₁₅H₁₅NO₄

139233-53-7

ziralimumabum

ziralimumab

immunoglobulin M, anti-(human antigen CD147) (human monoclonal

ABX-RB2 μ-chain), disulfide with human monoclonal ABX-RB2 light chain,

pentamer

immunomodulator

ziralimumab

immunoglobuline M, anti-(antigène CD147 humain) (chaîne μ de l’anticorps

monoclonal humain ABX-RB2), pentamère du disulfure avec la chaîne

légère de l’anticorps monoclonal humain ABX-RB2

immunomodulateur

ziralimumab

immunoglobulina M, anti-(antígeno CD147 humano) (cadena μ del anticuerpo

monoclonal humano ABX-RB2), pentámero del disulfuro con la cadena ligera

del anticuerpo monoclonal humano ABX-RB2

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

Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 61

p. 9 suprimase insértense
enalquireno enalkireno

Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 62
(Informaciones farmacéuticas de la OMS, Vol. 3, No. 4, 1989)

p. 5 suprimase insértense
ditequireno ditekireno

Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 70
(Información Farmacéutica OMS, Vol. 7, No. 4, 1993)

p. 14 suprimase insértense
zanquireno zankireno

Proposed International Nonproprietary Names (Prop. INN): List 83
Dénominations communes internationales proposées (DCI Prop.): Liste 83
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 83

p. 109 suprimase insértense
aliskiren aliskireno

p. 118 idraparinuxum natricum
idraparinux sódico sustitúyase la descripción por la siguiente:
O-2,3,4-tri-O-metil-6-O-sulfo-α-D-glucopiranosil-(1→4)-O-2,3-di-O-metil-β-
D-glucopiranuronosil-(1→4)-O-2,3,6-tri-O-sulfo-α-D-glucopiranosil-(1→4)-O-
2,3-di-O-metil-α-L-idopiranuronosil-(1→4)-2,3,6-tri-O-sulfo-α-D-
glucopiranósido de metilo nonasódico
p. 122 **supprimer**

norgestromine

**remplacer la description par la suivante:**

13-éthyl-17-hydroxy-18,19-dinor-17α-prégn-4-én-20-yn-3-one oxime

**delete/supprimer/suprimase**

ocinoxatum

ocinoxate

ocinoxato

p. 124 **oritavacinum**

oritavancine

**remplacer la description par la suivante:**


p. 125 **insert/insérer/insértese**

ozogamicinum

p. 126 **paliperidonum**

palipéridone

**remplacer la description par la suivante:**

(9RS)-3-[2-[4-(6-fluoro-1,2-bensisoxazol-3-yl]pipéridin-1-yl]éthyl]-9-hydroxy-2-méthyl-6,7,8,9-tétrahydro-4H-pyrido[1,2-a]pyrimidin-4-one

p. 127 **paliperidone**

**replace the molecular formula by the following:**

**remplacer la formule brute par:**

**sustitúyase la fórmula molecular por:**

C_{23}H_{27}FN_{4}O_{3}
p. 128  **rostaporfinum**
rostaporfine
rostaporfina

*replace the CAS registry number by the following:*
remplacer le numéro dans le registre du CAS par:
sustitúyase el número de registro del CAS por:

284041-10-7

p. 130  **talaporfinum**

talaporfine
talaporfina

*replace the CAS registry number by the following:*
remplacer le numéro dans le registre du CAS par:
sustitúyase el número de registro del CAS por:

110230-98-3

p. 132  **suprimase**

bupropiona

*insértese*

bupropión
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 in the selection of recommended international nonproprietary names for pharmaceutical substances, in accordance with the World Health Assembly resolution WHA3.11:

1. Proposals for recommended international nonproprietary names shall be submitted to the World Health Organization on the form provided therefor.

2. Such proposals shall be submitted by the Director-General of the World Health Organization to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated for this purpose, for consideration in accordance with the “General principles for guidance in devising International Nonproprietary Names”, appended 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.

3. Subsequent to the examination provided for in article 2, the Director-General of the World Health Organization shall give notice that a proposed international nonproprietary name is being considered.

   A. Such notice shall be given by publication in the Chronicle of the World Health Organization and by letter to Member States and to national pharmacopoeia commissions or other bodies designated by Member States.

   (i) Notice may also be sent to specific 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 a 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 the World Health Organization is acting and refer to these rules of procedure.

   C. In forwarding the notice, the Director-General of the World Health Organization 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 the World Health Organization.

4. Comments on the proposed name may be forwarded by any person to the World Health Organization within four months of the date of publication, under article 3, of the name in the Chronicle of the World Health Organization.

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 the Chronicle of the World Health Organization.

   A. Such objection shall:

       (i) identify the person objecting;

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1 The title of this publication was changed to WHO Chronicle in January 1959. From 1987 onwards lists of INNs are published in WHO Drug Information.
(ii) state his interest in the name;

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

6. Where there is a formal objection under article 5, the World Health Organization 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 the World Health Organization of a substitute name or names, a name shall not be selected by the World Health Organization as a recommended international nonproprietary name while there exists a formal objection thereto filed under article 5 which has not been withdrawn.

7. Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Director-General of the World Health Organization shall give notice in accordance with subsection A of article 3 that the name has been selected by the World Health Organization as a recommended international nonproprietary name.

8. In forwarding a recommended international nonproprietary name to Member States under article 7, the Director-General of the World Health Organization 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, including prohibiting registration of the name as a trade-mark or trade-name.

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.

* 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, international nonproprietary names (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 employing a characteristic "stem" indicative of a common property of the members of a group. The reasons for, and the implications of, the change are fully discussed.
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 Guiding Principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use.1 Where a stem is shown without any hyphens it may be used anywhere in the name.

<table>
<thead>
<tr>
<th>Latin</th>
<th>English</th>
</tr>
</thead>
<tbody>
<tr>
<td>-acum</td>
<td>-ac anti-inflammatory agents of the ibufenac group</td>
</tr>
<tr>
<td>-actidum</td>
<td>-actide synthetic polypeptides with a corticotropin-like action</td>
</tr>
<tr>
<td>-adolum</td>
<td>-adol analgetics</td>
</tr>
<tr>
<td>-adol-</td>
<td>-adol-</td>
</tr>
<tr>
<td>-astum</td>
<td>-ast antiasthmatic, antiallergic substances not acting primarily as antihistaminics</td>
</tr>
<tr>
<td>-astinum</td>
<td>-astine antihistaminics</td>
</tr>
<tr>
<td>-azepumum</td>
<td>-azepam diazepam derivatives</td>
</tr>
<tr>
<td>-bactumum</td>
<td>-bactam ( \beta )-lactamase inhibitors</td>
</tr>
<tr>
<td>bol</td>
<td>bol steroids, anabolic</td>
</tr>
<tr>
<td>-buzonum</td>
<td>-buzone anti-inflammatory analgesics, phenylbutazone derivatives</td>
</tr>
<tr>
<td>-cain-</td>
<td>-cain- antifibrillant substances with local anaesthetic activity</td>
</tr>
<tr>
<td>-cainum</td>
<td>-caine local anaesthetics</td>
</tr>
<tr>
<td>cef-</td>
<td>cef- antibiotics, cefalosporanic acid derivatives</td>
</tr>
<tr>
<td>-cillinum</td>
<td>-cillin antibiotics, derivatives of 6-aminopenicillanic acid</td>
</tr>
<tr>
<td>-conazolum</td>
<td>-conazole systemic antifungal agents, miconazole derivatives</td>
</tr>
<tr>
<td>cort</td>
<td>cort corticosteroids, except prednisolone derivatives</td>
</tr>
<tr>
<td>-dipinum</td>
<td>-dipine calcium channel blockers, nifedipine derivatives</td>
</tr>
<tr>
<td>-fibratum</td>
<td>-fibrate clofibrate derivatives</td>
</tr>
<tr>
<td>gest</td>
<td>gest steroids, progestogens</td>
</tr>
<tr>
<td>gli-</td>
<td>gli- sulfonamide hypoglycaemics</td>
</tr>
<tr>
<td>io-</td>
<td>io- iodine-containing contrast media</td>
</tr>
<tr>
<td>-ium</td>
<td>-ium quaternary ammonium compounds</td>
</tr>
<tr>
<td>-metacinum</td>
<td>-metacin anti-inflammatory substances, indometacin derivatives</td>
</tr>
<tr>
<td>-mycinum</td>
<td>-mycin antibiotics, produced by \textit{Streptomyces} strains</td>
</tr>
<tr>
<td>-nidazolum</td>
<td>-nidazole antiprotozoal substances, metronidazole derivatives</td>
</tr>
<tr>
<td>-ololum</td>
<td>-olol ( \beta )-adrenoceptor antagonists</td>
</tr>
<tr>
<td>-oxacinum</td>
<td>-oxacin antibacterial agents, nalidixic acid derivatives</td>
</tr>
<tr>
<td>-pridum</td>
<td>-pride sulpiride derivatives</td>
</tr>
<tr>
<td>-pril(at)um</td>
<td>pril(at) angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>-profenum</td>
<td>-profen anti-inflammatory substances, ibuprofen derivatives</td>
</tr>
<tr>
<td>prost</td>
<td>prost prostaglandins</td>
</tr>
<tr>
<td>-relinum</td>
<td>-relin hypophyseal hormone release-stimulating peptides</td>
</tr>
<tr>
<td>-terolum</td>
<td>-terol bronchodilators, phenthylamine derivatives</td>
</tr>
<tr>
<td>-tidinum</td>
<td>-tidine histamine ( \mathrm{H} )\textsubscript{2}-receptor antagonists</td>
</tr>
<tr>
<td>-trexatum</td>
<td>-trexate folic acid antagonists</td>
</tr>
<tr>
<td>-verinum</td>
<td>-verine spasmyotics with a papaverine-like action</td>
</tr>
<tr>
<td>vin-</td>
<td>vin- vinca alkaloids</td>
</tr>
</tbody>
</table>

\[1\] A more extensive listing of stems is contained in the working document \textit{WHO/EDM/QSM 99.6} 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
RECOMMANDÉES POUR LES SUBSTANCES PHARMACEUTIQUES*

L’Organisation mondiale de la Santé 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:

1. Les propositions de dénominations communes internationales recommandées sont soumises à l’Organisation mondiale de la Santé sur la formule prévue à cet effet.

2. Ces propositions sont soumises par le Directeur général de l’Organisation mondiale de la Santé aux experts désignés à cette fin parmi les personnalités inscrites au Tableau d’experts de la Pharmacopée internationale et des Préparations pharmaceutiques; elles sont examinées par les experts conformément aux “Directives générales pour la formation des dénominations communes internationales”, reproduites ci-après. 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.

3. Après l’examen prévu à l’article 2, le Directeur général de l’Organisation mondiale de la Santé notifie qu’un projet de dénomination commune internationale est à l’étude.

A. Cette notification est faite par une insertion dans la Chronique de l’Organisation mondiale de la Santé et par l’envoi d’une lettre aux Etats Membres et aux commissions nationales de pharmacopée ou autres organismes désignés par les Etats Membres.

(i) Notification peut également être faite à toute personne 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’Organisation mondiale de la Santé et référence au présent règlement.

C. En envoyant cette notification, le Directeur général de l’Organisation mondiale de la Santé demande aux Etats Membres de prendre les mesures nécessaires pour prévenir l’acquisition de droits de propriété sur la dénomination proposée pendant la période au cours de laquelle cette dénomination est mise à l’étude par l’Organisation mondiale de la Santé.

4. Des observations sur la dénomination proposée peuvent être adressées à l’Organisation mondiale de la Santé par toute personne, dans les quatre mois qui suivent la date de publication de la dénomination dans la Chronique de l’Organisation mondiale de la Santé (voir l’article 3).


1 Depuis janvier 1959, cette publication porte le titre de Chronique OMS. A partir de 1987, les listes des DCIs sont publiées dans les Informations pharmaceutiques OMS.
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 la *Chronique de l’Organisation mondiale de la Santé* (voir l’article 3).

A. Cette objection doit s’accompagner des indications suivantes:

   i) nom de l’auteur de l’objection;

   ii) intérêt qu’il porte à la dénomination en cause;

   iii) raisons motivant l’objection contre la dénomination proposée.

6. Lorsqu’une objection formelle est formulée en vertu de l’article 5, l’Organisation mondiale de la Santé 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 elle d’une ou de plusieurs appellations de remplacement, l’Organisation mondiale de la Santé 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.

7. Lorsqu’il n’est formulé aucune objection en vertu de l’article 5 ou que toutes les objections présentées ont été levées, le Directeur général de l’Organisation mondiale de la Santé fait une notification conformément aux dispositions de la sous-section A de l’article 3, en indiquant que la dénomination a été choisie par l’Organisation mondiale de la Santé en tant que dénomination commune internationale recommandée.

8. En communiquant aux Etats Membres, conformément à l’article 7, une dénomination commune internationale recommandée, le Directeur général de l’Organisation mondiale de la Santé:

   A. demande que cette dénomination soit reconnue comme dénomination commune de la substance considérée, et

   B. demande aux Etats Membres de prendre les mesures nécessaires pour prévenir l’acquisition de droits de propriété sur cette dénomination, notamment en interdisant le dépôt de cette dénomination comme marque ou appellation commerciale.

**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 apppellations déjà couramment employées.

2. La DCI de chaque substance devra, si possible, indiquer sa parenté pharmacologique. Les dénominations sus-ceptibles d’évoquer pour les malades des considérations anatomicques, physiologiques, pathologiques ou théra-peutiques devront être évitées dans la mesure du possible.

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

*Dans son vingtième rapport (Série de Rapports techniques de l’OMS, No. 581, 1975), le Comité OMS d’experts des Dénominations communes pour les Substances pharmaceutiques a examiné les directives générales pour la formation des dénominations communes internationales et la procédure à suivre en vue de leur choix, compte tenu de l’évolution du secteur pharmaceutique au cours des dernières années. La modification la plus importante a été l’extension aux substances de synthèse de la pratique normalement suivie pour désigner les substances tirées ou dérivées de produits naturels. Cette pratique consiste à employer des syllabes communes ou groupes de syllabes communes (segments clés) qui sont caractéristiques et indiquent une propriété commune aux membres du groupe des substances pour lequel ces segments clés ont été retenus. Les raisons et les conséquences de cette modification ont fait l’objet de discussions approfondies.*
3. Lorsqu’on formera la DCI de la première substance d’un nouveau groupe pharmacologique, on tiendra compte de la possibilité de former ultérieurement d’autres DCI appropriées pour les substances apparentées du même groupe.

4. Pour former des DCI des acides, on utilisera de préférence un seul mot. Leurs sels devront être désignés par un terme qui ne modifie pas le nom de l’acidé 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’acidé actif). Les dénominations pour différents sels ou esters d’une même substance active ne différeront que par le nom de l’acidé inactif (ou de la base inactive).

En ce qui concerne les substances à base d’ammonium quaternaire, la dénomination s’appliquera de façon appropriée au cation et à l’anion en tant qu’éléments distincts d’une substance quaternaire. On évitera de choisir une désignation évoquant un sel aminé.

6. On évitera d’ajouter une lettre ou un chiffre isolé; en outre, on renoncera de préférence au trait d’union.

7. Pour simplifier la traduction et la prononciation des DCI, la lettre “l” sera utilisée à la place de “ph”, “t” à la place de “th”, “e” à la place de “ae” ou “oe” et “i” à la place de “y”; l’usage des lettres “h” et “k” sera aussi évité.

8. On retiendra de préférence, pour autant qu’elles respectent les principes énoncés ici, les dénominations proposées par les personnes qui ont découvert ou qui, les premières, ont fabriqué et lancé sur le marché les préparations pharmaceutiques considérées, ou les dénominations déjà officiellement adoptées par un pays.

9. La parenté entre substances d’un même groupe (voir Directive générale 2) sera si possible indiquée dans les DCI par l’emploi de segments clés communs. La liste ci-après contient des exemples de segments clés pour des groupes de substances, surtout pour des groupes récents. Il y a beaucoup d’autres segments clés en utilisation active.

Les segments clés indiqués sans trait d’union pourront être insérés n’importe où dans une dénomination.

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1 Une liste plus complète de segments clés est contenue dans le document de travail WHO/EDM/QSM 99.6 qui est régulièrement mis à jour et qui peut être demandé auprès du Programme des DCI, OMS, Genève.
Anexo 1

PROCEDIMIENTO DE SELECCION DE DENOMINACIONES COMUNES INTERNACIONALES RECOMENDADAS PARA LAS SUSTANCIAS FARMACEUTICAS

La Organización Mundial de la Salud seguirá el procedimiento que se expone a continuación para la selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas, de conformidad con lo dispuesto en la resolución WHA3.11 de la Asamblea Mundial de la Salud:

1. Las propuestas de denominaciones comunes internacionales recomendadas se presentarán a la Organización Mundial de la Salud en los formularios que se proporcionen a estos efectos.

2. Estas propuestas serán sometidas por el Director General de la Organización Mundial de la Salud a los Miembros del Cuadro de Expertos de la Farmacopea Internacional y las Preparaciones Farmacéuticas encargados de su estudio, 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, fabricado o puesto a la venta por primera vez una sustancia farmacéutica.

3. Una vez terminado el estudio a que se refiere el artículo 2, el Director General de la Organización Mundial de la Salud notificará que está en estudio un proyecto de denominación internacional.

A. Esta notificación se hará mediante una publicación en la Crónica de la Organización Mundial de la Salud y el envío de una carta a los Estados Miembros y a las comisiones nacionales de las farmacopeas u otros organismos designados por los Estados Miembros.

(i) La notificación puede enviarse también a las personas que tengan un interés especial en una denominación objeto de estudio.

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2 Denominada Crónica de la OMS desde enero de 1959. A partir de 1987, las listas de DCI se publican en Información Farmacéutica OMS.
B. En estas notificaciones se incluyen los siguientes datos:

(i) denominación sometida a estudio;

(ii) nombre de la persona que ha presentado la propuesta de denominación de la sustancia si lo pide esta persona;

(iii) definición de la sustancia cuya denominación está en estudio;

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

(v) mención de los poderes conferidos para el caso a la Organización Mundial de la Salud y referencia al presente procedimiento.

C. Al enviar esta notificación, el Director General de la Organización Mundial de la Salud solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de propiedad sobre la denominación propuesta, durante el período en que la Organización Mundial de la Salud tenga en estudio esta denominación.

4. Toda persona puede formular a la Organización Mundial de la Salud observaciones sobre la denominación propuesta, dentro de los cuatro meses siguientes a su publicación en la Crónica de la Organización Mundial de la Salud, conforme a lo dispuesto en el artículo 3.

5. Toda persona interesada puede presentar una objeción formal contra la denominación propuesta, dentro de los cuatro meses siguientes a su publicación en la Crónica de la Organización Mundial de la Salud, conforme a lo dispuesto en el artículo 3.

A. Esta objeción deberá acompañarse de los siguientes datos:

i) nombre de la persona que formula la objeción;

ii) causas que motivan su interés por la denominación, y

iii) causas que motivan su objeción a la denominación propuesta.

6. Cuando se haya presentado una objeción formal en la forma prevista en el artículo 5, la Organización Mundial de la Salud puede someter a nuevo estudio la denominación propuesta, o bien utilizar sus buenos oficios para lograr que se retire la objeción. Sin perjuicio de que la Organización Mundial de la Salud estudie una o varias denominaciones en sustitución de la primitiva, ninguna denominación podrá ser seleccionada por la Organización Mundial de la Salud como denominación común internacional recomendada en tanto que exista una objeción formal, presentada como previene el artículo 5, que no haya sido retirada.

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, el Director de la Organización Mundial de la Salud notificará, conforme a lo dispuesto en el párrafo A del artículo 3, que la denominación ha sido seleccionada por la Organización Mundial de la Salud como denominación común internacional recomendada.

8. Al comunicar a los Estados Miembros una denominación común internacional conforme a lo previsto en el artículo 7, el Director General de la Organización Mundial de la Salud:

A. solicitará que esta denominación sea reconocida como denominación común para la sustancia de que se trate, y

B. solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de propiedad sobre la denominación, incluso la prohibición de registrarla como marca de fábrica o como nombre comercial.
Anexo 2

PRINCIPIOS GENERALES DE ORIENTACIÓN PARA FORMAR DENOMINACIONES COMUNES INTERNACIONALES PARA SUSTANCIAS FARMACÉUTICAS*

1. Las Denominaciones Comunes Internacionales (DCI) deberán diferenciarse tanto fonéticamente como ortográficamente. No deberán ser inómodamente 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 los nombres que puedan inducir fácilmente en el paciente sugestiones anatómicas, fisiológicas, patológicas o terapéuticas.

Estos principios primarios deberán ser tenidos en cuenta al aplicar 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 formar DCI convenientes para las sustancias emparentadas que vengan a incrementar el nuevo grupo.

4. Al idear DCI para ácidos, se preferirán las de una sola palabra; sus sales deberán denominarse sin modificar el nombre de ácido; p. ej., “oxacilina” y “oxacilina sódica”, “ibufenaco” e “ibufenaco sódico”.

5. Las DCI para las sustancias que se usan en forma de sal, deberán en general aplicarse a la base activa o, respectivamente, al ácido activo. Las denominaciones para diferentes sales o ésteres de la misma sustancia activa solamente deberán diferir en el nombre de 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 una letra o un número 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 que se sugieran estén de acuerdo con estos principios, recibirán una consideración preferente las denominaciones propuestas por la persona que haya descubierto la sustancia, o la que primeramente fabrique o ponga a la venta la sustancia farmacéutica, así como las denominaciones oficialmente adoptadas en cualquier país.

9. En las DCI, la relación de grupo o parentesco (véanse los Principios Generales de Orientación, apartado 2) se indicará en lo posible utilizando una partícula común. En la lista siguiente se dan algunos ejemplos de estas partículas en relación con diversos grupos de sustancias, en particular los de nuevo cuño. Hay otras muchas partículas comunes en uso. Cuando la partícula no lleva ningún guión, cabe utilizarla en cualquier parte de la denominación.

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* En su 20° informe (OMS, Serie de Informes Técnicos, No. 581, 1975) el Comité de Expertos de la OMS en Denominaciones Comunes para Sustancias Farmacéuticas examina los principios generales de orientación para formar denominaciones comunes internacionales (DCI) y el procedimiento de selección de las mismas, teniendo en cuenta las novedades registradas en los últimos años en materia de preparaciones farmacéuticas. Entre las modificaciones, la más importante ha sido la extensión a las sustancias químicas sintéticas de la práctica reservada anteriormente para designar sustancias originarias o derivadas de productos naturales. Esta práctica consiste en emplear una partícula característica que indique una propiedad común a los miembros de un determinado grupo de sustancias. En el informe se examinan a fondo las razones de esta modificación y sus consecuencias.

† El documento de trabajo WHO/EDM/QSM 99.6, que se pone al día regularmente, contiene una lista más extensa de partículas comunes. Las personas que deseen recibirla deberán solicitar su envío al Programa DCI, OMS, Ginebra (Suiza).
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