WHO Drug Information

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Regulatory Issues

Drug regulation in 2006: vision and challenges

The Twelfth International Conference of Drug Regulatory Authorities (ICDRA) held in Seoul, Republic of Korea, from 3 to 6 April 2006 has once again provided drug regulators with a unique opportunity to meet and discuss the particular challenges of medicines regulation. The continuing need to harmonize and strengthen collaboration is underscored by the increasing complexity of the medicines market and technical skills needed to regulate innovative products. The latest ICDRA was hosted by the Korea Food and Drug Administration in collaboration with the World Health Organization. The event was highly appreciated by developed and developing countries for its continuing role in fostering a regulatory forum where matters of urgency and international relevance can be openly debated. On this occasion, the event led to adoption of the following recommendations which regulators consider important in assuring the quality, safety and efficacy of medical products.

International Conference of Drug Regulatory Authorities (ICDRA): recommendations

Access to medicines: new regulatory pathways for public health needs

1. In the assessment of products, particularly those developed for public health needs, countries should make use of new regulatory pathways provided by highly-evolved regulatory agencies in order to avoid duplication of effort. This would enable optimal use of limited resources.

2. In cooperation with well resourced regulatory agencies, WHO is urged to assist Member States to provide training on the best use of regulatory information on product approvals available in the public domain.

3. WHO should continue its efforts to prequalify active pharmaceutical ingredients for medicines for priority diseases, including HIV/AIDS, malaria and tuberculosis. Information concerning prequalified products and approved sites should continue to be made public in the form of WHO public inspection reports.

4. WHO should assist national regulatory agencies to develop innovative approaches to improve access to safe and effective essential medicines of quality which address public health needs.

Emerging diseases and crises management: regulatory challenges

1. The fight against emerging diseases requires global collaboration and multidisciplinary effort. Member states should ensure their national regulatory agencies are closely involved in national strategic decision making processes and are engaged as key stakeholders in national contingency planning. In this context, national regulatory agencies should develop business continuity plans and may also have a role in facilitating vaccine and pharmaceutical research and development, and development of blood screening tests.

2. WHO should take a leading role in the global preparedness for pandemic infections. Central to its role as the global leading health agency, WHO should cooperate with Member States to ensure transparency of epidemiological information, co-ordinate information and technology transfer on clinical trials and research and assist Member States through developing WHO standards for pre-marketing.
evaluation of pharmaceuticals developed for pandemic use. It is important for national regulatory agencies to find mechanisms to share clinical trial results and epidemiological data. National regulatory agencies should not allow the threat of pandemics to compromise the principles of safety, efficacy and quality of vaccines and pharmaceuticals being considered for licensing approval.

3. National regulatory agencies should ensure that robust post-marking surveillance systems are in place to ensure that pharmaceuticals approved during a pandemic will continue to be closely monitored and subject to further assessment of their safety, efficacy and quality. To achieve this, national regulatory agencies should work with, among others, authorities for disease surveillance and the vaccine and pharmaceutical industry as close partners.

4. During a pandemic, the demand for blood and blood products is likely to increase. On the other hand, there could be lack of blood donations because of high morbidity and mortality of prospective donors. WHO should assist Member States -when drawing up contingency plans to include measures to maintain the integrity of their blood transfusion system, the continued supply of blood and blood products, and maintain transparency and information sharing.

New challenges in safety of medicines

High-profile drug safety issues present numerous challenges for drug regulators. New ways to improve knowledge about benefit/risk assessment, methods of signal detection, and communications to health professionals and the public are continually being sought. Spontaneous adverse drug reaction reporting has long been the cornerstone of pharmacovigilance and continues to serve a vital function, but changes in public expectations and drug development are encouraging regulators to think about pharmacovigilance as early as possible in the product life cycle.

The aim of pharmacovigilance planning is to provide regulators with a proactive approach to filling in knowledge gaps, while also improving the probability of detecting important safety signals as early as possible. Ultimately, this will result in better treatment choices for patients as they and their caregivers will have better information upon which to make choices. Furthermore, the publication of various risk management guidances, the improvement of scientific methods of adverse event signal detection and better and earlier communication of drug safety concerns to health professionals and the public are being developed. In addressing challenges of obtaining quality adverse event reports, cooperation between regulatory agencies and communicating effectively with the public are foremost.

Member States should:

1. Develop ways to ensure early communication to the public when an emerging safety concern arises.

2. Give patients, healthcare professionals and consumers quick and easy access to the most up-to-date and accurate information on medicines.

3. Encourage participation in WHO activities for reporting and collecting adverse reactions to medicines and vaccines, and seek ways to enhance reporting rates.

4. Improve scientific methods of adverse event signal detection.

WHO and Member States should:

5. Encourage pharmacovigilance planning in all public health programmes wherever possible.

WHO should:

6. Encourage cooperation between regulatory authorities when a new signal emerges.

Herbal medicines: safety through quality

1. Quality control of herbal medicines is complicated and difficult, and high-technology could be of valuable support. However, when country capacity is limited, continued use of dependable basic technical methods and tests is recommended.

2. Governments should provide adequate support for clinical studies, since there are few clinical studies and appropriate approaches for the assessment of efficacy. WHO should
provide technical guidance of appropriate approaches for clinical studies and assessment of efficacy of herbal medicines.

3. Traditional medicine plays an important role in primary health care in many developing countries and countries should consider categorizing herbal medicines based on available knowledge and the literature. Relevant appropriate requirements should be established for the assessment of safety and efficacy for different categorized herbal medicines to reduce cost and expenditure and meet demands of accessibility and affordability.

4. A challenge for national health authorities is the lack of research information and data on herbal medicines. Sharing national information and experience, as well as setting up common accepted standards through bilateral recognition and through international and regional regulatory cooperation for herbal medicines should be considered. WHO should continue to provide support to international and regional regulatory cooperative initiatives for herbal medicines.

5. In order to ensure safe and effective use of traditional medicine, integration of traditional medicine into national health systems should be considered where appropriate.

**Good Review Practices**

1. WHO should continue supporting country efforts to improve regulatory review processes in the context of overall improvement and implementation of good regulatory practices. Special emphasis should be given to helping small regulatory authorities; existing models may need to be adapted to match the resources available.

2. Regulators should make efforts to implement good review practices in order to improve regulatory systems through the introduction of good regulatory practices. Regulators should consider the road map approach, standardized formats for dossiers, disclosure of information, use of outside consultants, and quality management systems as useful tools for the improvement of review practices.

**Bioequivalence: from science to practice**

During recent years, the concept of bioequivalence has developed and several new regulatory approaches and guidance documents have been created. WHO has developed a comprehensive updated package of regulatory guidelines in line with former ICDRA recommendations.

1. Countries intending to implement bioequivalence requirements should consider learning from other countries’ experience and take a risk based approach to implementing bioequivalence.

2. WHO is encouraged to assist Member States by providing training for regulators and industry on the implementation of the newly adopted WHO guidelines on the establishment of interchangeability (including guidelines on registration requirements to establish interchangeability of multisource (generic) pharmaceutical products, a proposal to waive in vivo bioequivalence requirements for some of the immediate release solid dosage forms in the WHO Model List of Essential Medicines, guidelines for organizations performing in vivo bioequivalence studies and a revised list of international comparator products).

**Regulation of blood and blood-derived products: global challenges**

Assurance of safe and adequate blood supplies nationally and regionally requires effective regulation and continuous vigilance. The preparation of blood components as well as plasma derivatives should be subject to established regulatory standards and controls. Essential elements of blood and blood product regulation include implementation and enforcement of good manufacturing practices (GMP), evaluation of blood donor screening tests, blood related drugs and medical devices, and the establishment of effective pharmacovigilance systems. In order to support development of these activities in countries with limited resources, it is essential to strengthen international approaches to regulation and to encourage the collaboration of national regulatory agencies at both regional and global levels.
1. Effective regulatory oversight is essential to ensure the quality and safety of blood and blood products. However, this cannot be achieved in the absence of a national legal framework and policy. Countries should take an active role in updating their respective legal provisions so that the implementation and enforcement of GMP for blood establishments can be made effective. WHO should provide, upon request, technical advice to those countries wishing to update legal provisions to strengthen the regulation of blood and blood products.

2. WHO should continue to give the highest priority to strengthening educational programmes and to providing training opportunities to support implementation and enforcement of GMP in national blood and plasma establishments. Appropriate guidance documents should be developed and/or updated. Countries should take an active role to ensure the implementation and enforcement of GMP for blood and plasma establishments as a prerequisite for consistent quality in the preparation of blood and blood products.

3. WHO should continue to enable/promote cooperative interaction among national and regional regulatory authorities. In particular, WHO should:
   - continue to support the development of a cooperative network for leading regulatory agencies, and
   - facilitate the creation of regional networks of national authorities involved in the regulation of blood and blood products in order to enhance the regulatory role and leverage technical expertise.

4. Countries should take an active role in the operation of networks and regional steering committees should be established to promote harmonization of national regulatory policies. Appropriate support should be provided to this activity by WHO.

5. WHO should promote and encourage the establishment of effective pharmacovigilance systems for blood and blood products and link these to existing pharmacovigilance systems for medicines. Countries should implement and enforce appropriate and well structured reporting mechanisms for serious or unexpected adverse reactions to blood and blood products, including infectious transmissions. To enable safety investigations, countries should implement and enforce traceability with linkage from blood donor to recipient and from recipient to blood donor.

6. Regulatory authorities should encourage scientific studies to establish medical evidence in support of product labelling for clinical use. Suboptimal use of blood and blood products leads to wastage of precious products and increases the risk of side effects for recipients.

7. WHO should continue to strengthen the development of international reference materials and standards for validation and control of blood donor screening tests, especially for detection of anti-hepatitis C and anti-HIV antibodies.

8. WHO should encourage the development of risk-based regulatory strategies. Countries should consider establishing mechanisms and share information in this regard.

**Role of regulators in control of advertising and promotion**

1. Regulators should strengthen their efforts to ensure that advertising and promotion is in accordance with the approved product information and respective national regulations. To this end, regulators should collaborate closely with industry, publishers, the media and consumers. Such co-regulation of promotion must be underpinned by sound legislation and regulatory sanctions. Sanctions should be made public.

2. The global nature of the Internet is difficult to regulate. Regulators need to work together to control sources of Internet advertising. In addition, regulators should provide independent consumer and prescriber information on the Internet to support the quality use of medicines. This information should be easy to locate and be recognizable by prescribers and consumers. WHO is requested to continue to support countries in this regard.

3. WHO should increase its efforts to disseminate and promote the WHO Ethical Criteria for Medicinal Drug Promotion, in particular the provisions to ban direct-to-consumer advertising of prescription-only medicines and regulate
free samples to medical doctors. These criteria need to be actively supported by national regulatory agencies and used as the basis for national regulations. In this regard there needs to be close alignment between the regulation of promotion of medicines, foods and cosmetics.

**Access to treatment for severe pain: what can regulators do?**

1. Regulators should make efforts to ensure that national regulatory frameworks do not impose an excessive (i.e. not prescribed by the respective international conventions) administrative and legal burden on achieving access to internationally controlled narcotic painkillers.

2. To achieve better access to narcotic painkillers, and primarily those on the Model List of Essential Medicines, regulators are encouraged to work closely with international organizations such as the International Narcotics Control Board (INCB) and WHO, as well as with national and local bodies involved in palliative care. All severe pain needs to be appropriately addressed therapeutically and especially severe pain in life-limiting illnesses (cancer, HIV/AIDS).

3. Regulators should seek proactive ways to collaborate with other national health authorities to improve access to painkillers controlled under international conventions from importation/manufacture, through secure distribution chains, rational prescribing and dispensing to patients. To cover the population in need, it is necessary to widen patient access to legitimate prescribers, taking into account the national specific situation, e.g. consideration should be given to allowing specialized palliative care nurses or clinical officers to prescribe oral morphine.

4. WHO should support countries in improving their regulatory systems in order to identify potential administrative and legal hurdles to access of narcotic painkillers and find ways to eliminate these without compromising control functions prescribed by international conventions.

5. WHO should contribute to organizing respective regional and national training courses and exchange information on effective interventions carried out by countries that have achieved improvement in making narcotic painkillers more accessible to patients in need.

**Pharmacoeconomics and regulation**

Pharmacoeconomics is a discipline established to relate and identify the benefits and costs of medicines therapies. In the public sector, the aim is to inform and support decision-making in purchasing, pricing or reimbursement of medicines and to aid in clinical choice and guidance. Some of the main challenges encountered in setting up pharmacoeconomic mechanisms include questions about the clinical data and legal/scientific issues, and availability of capacity/resources.

**Member States should:**

1. Strive for open access to clinical regulatory data.

2. Be transparent about the criteria used in decision-making. If pharmaco-economics is one of them, provide clear methodological guidance.

3. Consider the need for active comparator studies and outcome data (to allow rational use of medicines) in pre-/post-authorization phases of regulatory assessment.

4. Consider the possibility to initiating/supporting independent comparative outcome studies.

**WHO should:**

5. Assist in high-level awareness-building.

6. Assist in capacity building.

7. Support regional networks.

8. Provide guidance on basic pharmacoeconomic evaluation to the relevant national health authorities.

**Global challenges for regulation of vaccines and other biologicals**

Biological medicines are one of the fastest growing sectors of the pharmaceutical industry. Regulation of biologicals presents special challenges due to the specificities introduced by the biological nature of the products and...
processes. Problems include the inherently variable nature of the starting materials and production systems which at some stage are derived from, or use, living organisms. Certain products, such as attenuated vaccines, consist of live organisms. The test methods needed to characterize products are biological (bioassays) and thus require special standardization efforts. Biologics research by the regulator may be necessary. Batch-related problems or accidents associated with biologics have occurred and thus batch-by-batch regulatory review is necessary. Furthermore, the complexity of biologics is increasing and some potential applications, such as gene therapy or cell and tissue therapy, are at the very leading edge of scientific development. Finally, a paradigm shift is occurring where biologics, such as vaccines that will be used globally, are increasingly being manufactured and first licensed in countries with the highest disease burdens. This is placing extra responsibilities on regulators in such countries, often in the context of limited regulatory resources.

1. Countries are requested to ensure that biologics receive science-based, innovative, and special regulatory attention. Regulatory collaboration is encouraged to support regulatory research and, further, to support countries without comprehensive biologicals regulatory systems. WHO should facilitate the process through establishment of regional and global networks of regulators.

2. WHO is requested to develop global regulatory consensus and guidance for biosimilars, which are a reality in several countries and will be a major regulatory challenge in the years to come.

3. Countries are encouraged to establish regional networks of national control laboratories (NCLs) to overcome the constraints that NCLs are facing now and in the future. WHO is requested to facilitate the work of NCLs through a global review of batch release strategies.

4. Countries are requested to increase their support for the development, characterization and distribution of biological reference preparations, which are an essential tool in the regulation of biological medicines. WHO is requested to ensure sustainability of its international biological reference preparation programme.

5. Vaccines are increasingly being first trialed in countries with the highest disease burden. Countries should ensure that regulatory review of new vaccine applications includes the quality and pre-clinical, as well as clinical, parts of the dossiers. WHO should extend its support for capacity building to include quality and pre-clinical evaluation.

6. New combination vaccines are increasingly being produced in developing countries and present special regulatory challenges. WHO is requested to develop guidance on the quality, safety and efficacy evaluations of combination vaccines, including advice on bridging studies when combination vaccines are used in new populations.

**Stability: global challenges for harmonization**

Efforts regionally and interregionally to harmonize stability testing conditions offer many challenges, particularly for the hot and humid zone conditions. The question has generated much debate as to proper temperature and humidity conditions in relation to predicting the proper shelf life of a medicinal product within a country.

1. Member States should identify their stability testing conditions in order to facilitate import to and export from their country. Ideally these should be based on conditions currently in use, thus avoiding creation of barriers to access to medicines.

2. Member States should make information available to WHO regarding stability conditions to be used within their markets.

3. WHO should make available country information in order to facilitate accessibility by manufactures and any interested party on an international basis.

4. WHO should observe the stability situation and any future developments and continue its efforts to find harmonized conditions, in light of any major changes to the current situation in regions.
5. Any international mechanism or organization which develops guidance relevant for countries outside their own regions should ensure that those countries are made aware of these developments and are directly approached to take part in the consultation process. For the International Conference on Harmonization (ICH), the Global Cooperation Group should be stressed as a way to work with regional harmonization initiatives.

**Counterfeit medicines: toward better structured international collaboration**

The 12th ICDRA congratulates WHO for the conference organized in Rome in February 2006 following-up on the recommendations of the 11th ICDRA and endorses the Declaration of Rome.

The 12th ICDRA welcomes the establishment of the International Medical Products Anti-Counterfeiting Task Force (IMPACT) and congratulates WHO on establishment of the IMPACT Secretariat.

*The 12th ICDRA expects IMPACT to:*:

1. Work on the basis of terms of reference that should take into account the topics raised in the Rome Declaration and at the 12th ICDRA and should provide clear milestones and tangible results.

2. Develop concrete and pragmatic proposals on how to improve national, regional and international strategies to combat counterfeit medicines.

3. Analyse in particular how to improve the sharing of information on cases of counterfeit medicines taking into consideration existing systems, e.g. WHO Rapid Alert System.

4. Take into consideration existing activities in order to use the synergies of such activities and avoid duplication of effort.

5. The 12th ICDRA calls upon WHO to provide all necessary support to IMPACT via its Secretariat.

6. It calls upon the national and regional authorities to fully support IMPACT by providing the necessary resources during its work and by implementing its recommendations.

**Small model drug regulatory authorities**

1. Small national drug regulatory authorities (DRAs) should establish appropriate regulatory structures that correspond to the situation of the country without compromising minimum standards of safety, quality and efficacy, and should also attune legislative and administrative practices to the resources at the DRA’s disposal.

2. Regulatory activities should be prioritized to develop and build up the registration and regulatory system in a stepwise manner, but continue to expedite access of essential medicines to the country’s population.

3. Small DRAs should identify appropriate best practices for implementation that can be adopted or adapted to their situations by studying reference countries and suitable benchmark authorities.

4. Small DRAs should engage proactively in international cooperation, both at regional and global levels.

*WHO should:*

5. Consider convening a forum of small DRAs to facilitate sharing of information and best practices, including (a) leveraging on safety, quality and efficacy information available from larger, trusted authorities; (b) identifying trusted sources of generic medicines; and (c) standardizing formats for sharing of data about registered medicines in various national jurisdictions.

6. Continue to encourage the benefits of regional networks wherein smaller regulators can work with trusted larger regional authorities in order to optimize resources and enhance regulatory capacity.

**IPR for pharmaceuticals: improving or impeding access?**

The rationale for the protection of intellectual property rights (IPR) is the creation of incentives for technological innovation. However, IP protection may limit access to technologies and products because it creates monopolies and decreases competition in the market,
thereby allowing patent holders to set the prices. Neither can IPR protection (for example, as required under the TRIPS agreement), adequately address the interrelationship between incentives, IPR and innovation in pharmaceuticals. Patents on chemical compounds or molecules do not always necessarily result in priority disease drugs, or guarantee access to such drugs.

1. National regulatory agencies should contribute to ensuring the right balance between the need for innovation and equitable access, and between commercial and public health interests. To this end, they should closely collaborate with other ministries, the patent office and other national stakeholders in developing national patent legislation. However, regulatory agencies should not be involved in enforcement of patents as part of the process of regulatory decision making.

2. Countries should incorporate into their national legislation the relevant TRIPS flexibilities for export or supply of medicines of assured quality to countries with public health emergencies.

3. WHO should strengthen its capacity building to support countries in making maximum use of the TRIPS flexibilities.

The ICDRA Report and Recommendations are available on the WHO website at: http://www.who.int/medicines/icdra/en/index/html
Safety and Efficacy Issues

Tenofovir and nonsteroidal anti–inflammatories: acute renal failure

Canada — Tenofovir disoproxil fumarate (Viread®) is an antiretroviral indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in patients 18 years of age and older (1). Tenofovir was marketed on 15 March 2004. Nephrotoxicity, including renal failure, renal insufficiency, elevated creatinine level, hypophosphataemia and Fanconi syndrome, has been reported with the use of tenofovir in clinical practice, as indicated under warnings and precautions in the product monograph (1).

Health Canada has received 22 domestic reports of adverse reactions suspected of being associated with the use of tenofovir. Ten of these reports involved nephrotoxic reactions, three of which were observed when a nonsteroidal anti-inflammatory drug (NSAID) was added along with the antiretroviral therapy, which included tenofovir.

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion (1). Renal toxicity occurs with the accumulation of tenofovir in the proximal tubule and appears to be concentration dependent (2). Cases of renal failure with tenofovir have been reported in patients with no known risk factors (1). However, published case reports of nephrotoxicity suggest that there may be specific risk factors including pre-existing renal dysfunction, long duration of use, low body weight, concomitant use of drugs that may increase levels of tenofovir and other drug interactions (2–4). Long-standing HIV infection itself may lead to higher incidence of nephropathy (2).

Concurrent use of a nephrotoxic agent should be avoided with tenofovir, and the dosing interval should be adjusted in patients with a baseline creatinine clearance of less than 50 mL/min (1). NSAIDs are frequently used and are available over the counter. Since NSAIDs are potentially nephrotoxic, their use during tenofovir therapy may represent an additional risk for renal failure.

Extracted from the Canadian Adverse Reaction Newsletter. Volume 16, Issue 2, April 2006

References


Update on status of contraceptive skin patch

Canada — The results of two studies looking at the risk of serious side effects when using the Ortho Evra® contraceptive patch marketed in the United States are currently being reviewed. The version of Evra® marketed in Canada is manufactured differently and contains less estrogen than the US product.

A preliminary report on one of the studies shows an approximately twofold increase in the risk of blood clots compared with users of an oral contraceptive. However, the second study concludes that the risk of non-fatal blood clots with the patch is similar to the risk of comparable oral contraceptives. Both studies, one of which is ongoing, were communicated to Health Canada by the manufacturer.

Blood clots are a relatively rare event but have been reported as a potential risk of all hormonal contraceptive therapy. Other serious side
effects being examined in the studies include heart attack and stroke. Once the review is complete, Health Canada will communicate any new safety information.

The current labelling information contains a description of the risks and a detailed section on the importance of discontinuing medication at the earliest sign of blood clots. Common symptoms for blood clots can include, but are not limited to, pain in the calf, shortness of breath, chest pain or coughing blood. Health Canada issued a previous statement regarding Evra on 28 November 2005.


SSRI antidepressants linked to lung disorder in newborns

Canada — Generally, selective serotonin re-uptake inhibitor (SSRI) treatment should only be continued during pregnancy if the benefits to the individual patient are thought to outweigh the risks to the unborn child, while also considering the benefits and risks of switching to another treatment option or stopping treatment altogether. SSRIs and other newer antidepressants prescribed for the treatment of depression include the following: bupropion, citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline and venlafaxine.

A study published recently in the New England Journal of Medicine suggests that use of SSRIs during the second half of pregnancy may be associated with a condition called persistent pulmonary hypertension of the newborn. Newborns with this rare but life-threatening condition do not receive enough oxygen in the blood and require intensive-care treatment to survive. According to the study, babies born with this condition were six times more likely than healthy babies to have been exposed to SSRIs. This information is considered to be preliminary at this time.

Numerous reports in Canada and abroad have already indicated that some children exposed to SSRIs and other newer antidepressants during pregnancy may develop serious complications at birth. An increase in the overall risk of major birth defects has also been associated with SSRI use.


ACE inhibitors and birth defects

Use of angiotensin-converting–enzyme (ACE) inhibitors during the second and third trimesters of pregnancy is contraindicated because of their association with an increased risk of fetopathy. In contrast, first-trimester use of ACE inhibitors has not been linked to adverse fetal outcomes. The results of a study to assess the association between exposure to ACE inhibitors during the first trimester of pregnancy only and the risk of congenital malformations have recently been published in the New England Journal of Medicine (1, 2).

ACE inhibitors are among the most widely prescribed antihypertensive agents, but when used in the second half of pregnancy, they can cause oligohydramnios, fetal growth retardation, pulmonary hypoplasia, joint contractures, hypocalvaria and neonatal renal failure, hypotension and death. These effects result from the blockade of the conversion of angiotensin I to angiotensin II in the developing fetal kidneys.

A cohort of 29 507 infants born between 1985 and 2000 for whom there was no evidence of maternal diabetes were enrolled. In the first trimester alone, 209 infants with exposure to ACE inhibitors were identified, 202 infants with exposure to other antihypertensive medications in the first trimester, and 29 096 infants with no exposure to antihypertensive drugs at any time during gestation. Major congenital malformations were identified from linked vital records and hospitalization claims during the first year of life and confirmed by review of medical records.

Infants with only first-trimester exposure to ACE inhibitors had an increased risk of major congenital malformations as compared with infants who had no exposure to antihypertensive medications. In contrast, fetal exposure to other antihypertensive medications during only the first trimester did not confer an increased risk. Infants exposed to ACE inhibitors were at increased risk for malformations of the cardiovascular system and the central nervous system. It was concluded that exposure to ACE inhibitors during the first trimester cannot be considered safe and should be avoided.
References

ACE inhibitors and pregnancy
United States of America — The New England Journal of Medicine (see above) has published an article reporting that infants whose mothers had taken an angiotensin-converting enzyme inhibitor (ACE inhibitor) during the first trimester of pregnancy had an increased risk of major congenital malformations, compared with infants who had not undergone first trimester exposure to ACE inhibitors. The number of cases of birth defects is small and the findings of this study have not yet been repeated (1).

According to the approved labels, ACE inhibitors are labelled as pregnancy category C for the first trimester of pregnancy and category D for the second and third trimesters. The existing prescribing information recommends discontinuing ACE inhibitors as soon as possible if a patient becomes pregnant. Because of the preliminary nature of the newly published data, the Food and Drug Administration (FDA) does not plan to change the pregnancy categories at this time (2), but healthcare professionals should take these findings into consideration with other information about a patient's medical situation during early pregnancy.

ACE inhibitors include: benazepril (Lotensin®), captopril (Capoten®), enalapril/enalaprilat (Vasotec® oral and injectable), fosinopril (Monopril®), lisinopril (Zestril® and Prinivil®), moexipril (Univasc®), perindopril (Aceon®), quinapril (Accupril®), ramipril (Altace®), and trandolapril (Mavik®)

References
1. FDA Alert/Public Health Advisory, 7 June 2006.

Gadolinium-containing contrast agents and nephrogenic systemic fibrosis
United States of America — The Food and Drug Administration (FDA) is evaluating important safety information about gadolinium-containing contrast agents and a disease known as nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy (NSF/NFD) that occurs in patients with kidney failure. New reports have identified a possible link between NSF/NFD and exposure to gadolinium-containing contrast agents used at high doses for a procedure called magnetic resonance angiography (MRA).

The FDA has learned of 25 cases of NSF/NFD in patients with kidney failure who received Omniscan®, a gadolinium-containing contrast agent following an MRA. The FDA is actively investigating whether exposure to a gadolinium-containing contrast agent for MRA is associated with the development of NSF/NFD. In the meantime, the following recommendations are being provided.

Gadolinium-containing contrast agents, especially at high doses, should be used only if clearly necessary in patients with advanced kidney failure. It may be prudent to institute prompt dialysis in patients with advanced kidney dysfunction who receive a gadolinium contrast MRA.

Five gadolinium-containing contrast agents are FDA-approved for use during magnetic resonance imaging (MRI): Omniscan®, OptiMARK®, Magnevist®, ProHance®, and MultiHance®. None of these drugs are FDA approved for MRA. The dose of gadolinium-containing contrast agent given to patients undergoing an MRA test is often higher (up to three times) than the approved dose for MRI.

NSF/NFD appears to occur in patients with kidney failure along with acidosis. Patients with NSF/NFD have tight and rigid skin making it difficult to bend joints. NSF/NFD may also result in fibrosis, or scarring, of body organs resulting in the inability of body organs to work properly and can lead to death. Scientists first identified NSF/NFD in 1997 and the cause of NSF/NFD is unknown. Worldwide, there are approximately 200 reports of NSF/NFD.
The 25 cases of NSF/NFD were reported in May 2006, by the Danish Medicines Agency. Among these, 20 cases occurred in Denmark and five cases occurred in Austria. The patients developed NSF/SFD within 3 months after receiving the gadolinium-containing contrast agent (2).

The FDA is gathering additional information about NSF/NFD and investigating whether other patients who received gadolinium-containing contrast agents developed NSF/NFD.

References

Gatifloxacin and blood glucose disturbances

Singapore — The Health Sciences Agency (HSA) would like to draw the attention of healthcare professionals to the known adverse effects of hypoglycaemia and hyperglycaemia associated with gatifloxacin (Tequin®), a fluoroquinolone antibiotic, and the recent contraindication on the use of the drug in patients with diabetes mellitus.

Serious cases of both hypoglycaemia and hyperglycaemia have been reported with gatifloxacin during post-marketing surveillance. From the overseas spontaneous postmarketing reports, it was noted that cases of blood glucose disturbances usually occurred in diabetic patients. There were very rare events of hypoglycaemia and hyperglycaemia which were life-threatening. In the majority of cases, the patients had other underlying medical problems and were receiving concomitant medications that may have contributed to the glucose abnormality. A few of these cases resulted in fatalities.

The patients particularly at risk include diabetics and the elderly (>75 years of age) who may have unrecognized diabetes, age-related decrease in renal function, underlying medical problems, and/or are taking concomitant medications associated with dysglycaemia. However, dysglycaemia has been reported to occur in patients without a history of diabetes.

Gatifloxacin has been demonstrated to be associated with transient disturbances in glucose homeostasis, including an increase in serum insulin and decrease in serum glucose following administration of initial doses. This is sometimes associated with symptomatic hypoglycaemia. In addition, increases in fasting serum glucose were observed, usually after the third day of gatifloxacin administration and continuing throughout the duration of treatment. The levels return to pre-dose values by 14 days after the completion of treatment.

To ensure the safe and effective use of gatifloxacin, the company is recommending a contraindication in patients with diabetes mellitus. Physicians are advised to closely monitor the blood glucose of nondiabetic patients who are at risk of dysglycaemic events for signs and symptoms of blood glucose disturbances. Risk factors include older age, renal insufficiency, drug interactions with glucose-altering medications (such as antidiabetic agents like glibenclamide). If signs and symptoms of either hypoglycaemia or hyperglycaemia occur in any patient treated with gatifloxacin, appropriate therapy should be initiated immediately and gatifloxacin should be discontinued.

References
Essential Medicines

WHO Model List of Essential Medicines and developed countries: a comparison with the Lothian Joint Formulary

Essential medicines lists and formularies are valuable public health tools which balance consideration of need, efficacy, safety and cost. The WHO Model List of Essential Medicines has been widely adopted or adapted in over 150 countries, and it has been suggested that industrialized countries should incorporate the Essential Medicines concept into their health policy. This summary describes a comparative study conducted to investigate whether the WHO Model List of Essential Medicines is suitable as a basis for generating or reviewing a formulary in the industrialized world. It builds on a critical analysis of the WHO Model List of Essential Medicines and the Scottish Lothian Joint Formulary and determines, in particular, the relevance of the List for developed countries.

Essential medicines concept and the WHO Model List

There is great disparity between the health care expenditure of developing and industrialized countries. In high-income countries, medicines account for less than 15% of overall health care expenditure compared with 25–70% in developing countries (1). It was within this climate that the concept of essential medicines was introduced in 1977 with the publication of the first WHO Model List of Essential Medicines (EML) (2).

Essential medicines are defined as “those that satisfy the priority health needs of the population.” It is a national responsibility to identify which medicines are “essential”, with selection dependent on disease prevalence, evidence of efficacy and safety, and comparative cost-effectiveness. Essential medicines should be affordable, of assured quality, and available at all times within functioning health systems in adequate amounts and appropriate dosage forms. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations.

The EML is composed of a core list and a complementary list (3). The core list is “a list of minimum medicine requirements for a basic health care system.” It contains the most efficacious, safe and cost-effective medicines for priority diseases, which are based on current and predicted public health relevance, with potential for safe and cost-effective treatment. The complementary list contains “essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed.”

In the EML, a square box symbol indicates that there are many possible medicines within a specific therapeutic class that can be used to treat a given condition (2, 4). This symbol was introduced in recognition of the global variation that can occur in the availability and cost of medicines. A medicine included in the EML is the one of that class for which there is the best evidence for effectiveness and safety. It may be the first to be marketed, or a safer or more effective newer medicine. Alternatively, if there is no difference in efficacy and safety, the least expensive medicine.

* Article based on “A comparison of the WHO Model List of essential medicines and the Lothian Joint Formulary”, a study conducted by Ms Sharon Hems, Lothian Joint Formulary Pharmacist, St John’s Hospital, Livingston, Scotland (available from Sharon.Hems@isd.csa.scot.nhs.uk) and Dr Richard Laing, Department of Medicines Policy and Standards, World Health Organization, Geneva
Role of formularies
The essential medicines process is comparable to many systems adopted by industrialized countries to develop formularies. Formularies are restricted lists of medicines from which appropriate therapy can be selected, and are aimed to encourage safe, appropriate and cost-effective prescribing. Information regarding doses, indications, adverse effects, contraindications and warnings for medicines in the EML is contained in the WHO Model Formulary (5). The WHO Model Formulary does not provide information on comparative costs or additional medicines.

The Lothian Joint Formulary (LJF) (7) was first produced in 2001 to serve a population in the Edinburgh area of 770,000, with 530 General Practitioners in 130 practices, 140 community pharmacies, two large teaching hospitals, one paediatric hospital and one district general hospital. Annual medicines expenditure in primary care is currently in excess of £120 million.

The LJF is intended to be used in conjunction with the British National Formulary (BNF) (6), which provides further information on side-effects, drug interactions, costs, and more comprehensive information on a wider range of medicines.

The WHO Expert Committee on the Selection and Use of Essential Medicines has developed a transparent submission and review web-based process. If the data produced in this process could also be used by the Lothian Formulary Committee, this could improve the efficiency of the selection process. If the EML process is suitable as a basis for generating or reviewing a formulary in the industrialized world, this could benefit both members of the WHO Expert Committee and formulary committees (8, 9).

The selection of medicines for inclusion in the EML or the LJF will depend on disease burden, and evidence of efficacy, safety and comparative cost-effectiveness. If appropriate, drug stability, the need for special diagnostic or treatment facilities, and pharmacokinetic properties may also be considered. The EML is intended as a starting point for national governments and institutions to develop their own formularies and a number of factors may be taken into account when they adapt the EML, such as:

- local demography and pattern of diseases;
- training and experience of available personnel;
- local availability of medicines;
- financial resources; and
- environmental factors.

In Lothian, formulary working groups have used historical prescribing patterns to provide an insight into how drugs were used locally and highlight prescribing areas of concern. Additional factors considered by the Lothian Formulary Committee are the patent status of the medicine, and information on anticipated use and overall cost. Recommendations produced by the Scottish Medicines Consortium (SMC) will influence the inclusion of newly licensed medicines, and new formulations or indications. However, the Committee will also consider applications for unlicensed medicines or medicines used outside their licensed indications. In addition, there is a process in place for appeal against decisions.

In contrast to the EML, the LJF specifies first and second choice medicines for the treatment of common conditions occurring in primary and secondary care and it therefore does not contain many medicines for the treatment of poisoning, nor sections on blood products, immunologicals or peritoneal dialysis, as in the EML. The LJF aims to cover approximately 80% of prescribing situations, and includes dosing information and prescribing notes to highlight key messages regarding the medicines or conditions being treated (7).

The majority of medicines contained in the LJF and the EML are single compounds. Combination products may be selected if they have a proven advantage in therapeutic effect, safety or adherence compared to the individual compounds administered separately. For example, the WHO Expert Committee encourages the use of fixed-dose combination products for the treatment of HIV/AIDS, tuberculosis and malaria to decrease the emergence of drug resistance (3).

Differences between the EML and LJF
The LJF provides guidance on commonly occurring disorders in Lothian, which will differ from those in developing countries. For
instance, the leading causes of death and morbidity in Africa, Asia and South America are HIV/AIDS, tuberculosis, malaria and respiratory infections (10, 11). This is reflected in the choice of medicines in the EML, which contains substantially more medicines (107) for the treatment of infections than the LJF (31). Infectious diseases are also the most common cause of death worldwide, followed by cardiovascular diseases, maternal and perinatal conditions, respiratory infections and cancers (1). Within the UK, however, circulatory diseases (including heart disease and stroke) and cancer are the two most common causes of death (12).

Another factor that influences the choice of medicines is the age distribution of the population. In some African countries, average life expectancy has dropped below 40 due to HIV/AIDS (13). Almost 20% of global deaths in 2002 were children aged less than 5 years of which 98% occurred in developing countries (12). The main causes are infectious and parasitic diseases partly as a result of the HIV/AIDS epidemic.

It is also reported that more than 60% of deaths in developed countries occur beyond age 70, compared with about 30% in developing countries (12). Diseases which occur predominantly in older people, such as osteoarthritis, dementia, ischaemic heart disease and cerebrovascular disease, will therefore be observed more frequently in the United Kingdom than in developing countries. In addition, the LJF contains medicines for the treatment of lifestyle illnesses such as smoking or obesity. It would be expected that patient demand and expectation, which can influence prescribing of medicines for these conditions in developed countries, would be different in developing countries. However, there are sections within the LJF which may be appropriate for inclusion in the EML such as ear, nose and throat (ENT), oral nutrition and genito-urinary disorders.

In Scotland, it has been estimated that substituting premium-priced products with cheaper standard alternatives could result in a potential saving of £5.8 million (14). The contrast in the number of formulations may also suggest that the range of formulations in the EML should be revised, in particular for paediatric formulations (25).

The LJF has an advantage in being a dynamic document which is continually revised and updated to reflect evidence-based medicine as well as local expertise and practice. Since the EML is updated every 2 years there is a risk that some recommendations could be out of date. An electronic consultative mechanism

Table 1: Content of the EML and the LJF

<table>
<thead>
<tr>
<th>Content</th>
<th>EML</th>
<th>LJF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of medicines (including duplicate entries)</td>
<td>369</td>
<td>531</td>
</tr>
<tr>
<td>Number of medicines by name only (not including duplicate entries)</td>
<td>311</td>
<td>417</td>
</tr>
<tr>
<td>Number of medicines common to EML and LJF (by medicine name only, excluding duplicates)</td>
<td>45% (139) of medicines in EML are in LJF</td>
<td>33% (139) of medicines in LJF are in EML</td>
</tr>
<tr>
<td>Number of medicines common to EML and LJF (considering section, including duplicates)</td>
<td>41% (153)</td>
<td>29% (153)</td>
</tr>
<tr>
<td>Number of formulations (including duplicates)</td>
<td>622</td>
<td>1412</td>
</tr>
<tr>
<td>Average number of formulations per medicine</td>
<td>1.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Number of medicines with a square box</td>
<td>25%</td>
<td>N/A</td>
</tr>
</tbody>
</table>
is needed to cope with such eventualities, and
to enable changes to be made to the EML
more rapidly.

One of the major advantages of the WHO
Expert Committee is the transparency of its
decision-making processes. This makes it
possible to identify the rationale behind the
addition or removal of medicines from the
EML, and therefore help facilitate local
decisions with regard to this advice. However,
there has been concern regarding the imple-
mentation of recommendations. For example,
magnesium sulphate was added to the EML in
1997 for the treatment of eclampsia and pre-
eclampsia. Despite this, however, it is still not
available in many low and middle-income
countries, and clinical guidelines have been
poorly implemented (16, 17). An implementa-
tion strategy, including promotion of formulary
recommendations and provision of feedback
to prescribers on formulary adherence, has
been developed in Lothian to increase
awareness and use of the LJF, and a similar
approach may benefit WHO.

Proposals for action
This study revealed interesting differences in the
processes and products of the EML and the LJF.
The decision-making processes of the two com-
mittees are similar but the WHO Expert Com-
mittee benefits from a more transparent and
clearly documented process. There would be
advantages, however, in reviewing the EML

Table 2: Number of medicines in each section of the EML and the LJF

<table>
<thead>
<tr>
<th>Section</th>
<th>No. in EML</th>
<th>No. in LJF</th>
<th>No. in both EML &amp; LJF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anaesthetics</td>
<td>13</td>
<td>21</td>
<td>53</td>
</tr>
<tr>
<td>2. Analgesics, DMARDs</td>
<td>11</td>
<td>30</td>
<td>39</td>
</tr>
<tr>
<td>3. Antiallergics, anaphylaxis</td>
<td>5</td>
<td>7</td>
<td>83</td>
</tr>
<tr>
<td>4. Poisoning</td>
<td>14</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>5. Antiepileptics</td>
<td>7</td>
<td>12</td>
<td>53</td>
</tr>
<tr>
<td>6. Infection</td>
<td>107</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>7. Migraine</td>
<td>3</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>8. Cancer, palliative care</td>
<td>26</td>
<td>59</td>
<td>45</td>
</tr>
<tr>
<td>9. Parkinsons</td>
<td>2</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>10. Blood</td>
<td>8</td>
<td>16</td>
<td>50</td>
</tr>
<tr>
<td>11. Blood prods</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12. CVS</td>
<td>25</td>
<td>49</td>
<td>43</td>
</tr>
<tr>
<td>13. Skin</td>
<td>21</td>
<td>53</td>
<td>27</td>
</tr>
<tr>
<td>14. Diagnostic</td>
<td>8</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>15. Disinfectants</td>
<td>6</td>
<td>3</td>
<td>44</td>
</tr>
<tr>
<td>16. Diuretics</td>
<td>5</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>17. GI</td>
<td>11</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>18. Endocrine</td>
<td>19</td>
<td>59</td>
<td>33</td>
</tr>
<tr>
<td>19. Immunologicals</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20. Muscle relaxants, cholinesterase inhibitors</td>
<td>5</td>
<td>9</td>
<td>57</td>
</tr>
<tr>
<td>21. Eye</td>
<td>10</td>
<td>26</td>
<td>33</td>
</tr>
<tr>
<td>22. Oxytocics, antioxytocics</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>23. Peritoneal dialysis</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>24. Psychotherapeutic medicines</td>
<td>10</td>
<td>37</td>
<td>34</td>
</tr>
<tr>
<td>25. Respiratory</td>
<td>4</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>26. Electrolyte</td>
<td>9</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>27. Vitamins and minerals</td>
<td>10</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>28. ENT</td>
<td>-</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>29. Oral nutrition</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>30. Genitourinary disorders</td>
<td>-</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>369</strong></td>
<td><strong>531</strong></td>
<td><strong>17%</strong></td>
</tr>
</tbody>
</table>
more frequently and introducing an implement-
strategy similar to that developed in Lo-
thian.

Some important points for consideration
• The decision-making processes of Drug and
  Therapeutics or Formulary Committees
  should be transparent and clearly docu-
  mented.
• Frequent review and an implementation
  strategy are necessary to ensure that
  formularies are up to date and used in
  practice.
• When the WHO Model List of Essential
  Medicines is published every two years,
  formulary committees could compare their
  list with the EML according to the methods
  described in this study.
• The WHO Model List of Essential Medicines
  is a useful tool for the review of a formulary
  but is not suitable for adoption, without
  adaptation, within the industrialised world.
• The WHO electronic library is a useful
  resource and the decisions of the WHO
  Expert Committee should be considered by
  Drug and Therapeutics or Formulary
  Committees.

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    ing research into policy and practice in developing
    countries: a case study of magnesium sulphate for
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    2005; 5: 68.
Adherence to WHO’s Model List of Essential Medicines in two European countries

The concept of Essential Medicines is one of the most important tools available for improving public health in developing countries and key elements include the WHO Model List of Essential Medicines (1, 2). It has been proposed that developed countries could also make use of the Model List to a greater extent, in particular to promote better quality of care and control drug expenditure (2). However, the applicability of the Essential Medicines concept for industrialized countries has been questioned and there is a lack of studies analysing the use of the Model List in this context (3).

In this article, adherence to the 2003 WHO Model List of Essential Medicines (EML) was analysed through an observational study of medicines use in outpatient care in two European countries — Croatia and Sweden. Data on dispensed prescriptions and over-the-counter (OTC) drugs were collected from wholesalers in Croatia and pharmacies in Sweden. WHO Collaborating Centres in Norway and Sweden have developed and apply several methodologies to evaluate drug use and quality of drug utilization patterns. In the study, analyses focused on medicines accounting for 90% of use in Defined Daily Doses (DU90%). DU90% profiles provide a quick method to overview and evaluate potential for improvement while offering a reflection on the relevance and appropriateness of the WHO Model List of Essential Medicines.

Drug use and utilization: new challenges for the WHO Model List of Essential Medicines

The WHO Model List of Essential Medicines (EML) includes about 300 drugs intended to provide safe and effective treatment for the majority of diseases (4). The selection of medicines is based on disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness: basically the same principles that have been applied by Drug and Therapeutics Committees for many years (5).

The medicines included in the EML are intended to be available at all times in adequate amounts, in appropriate dosage forms, with assured quality, and at a price the individual and the community can afford (3). The EML is useful both from a medical and an economical point of view as a tool for information, prescriber training and medical audit as well as to simplify procurement, drug distribution and reimbursement (2).

Rational drug use has been defined as the act of patients receiving medication appropriate to their medical needs, in doses meeting their own individual requirements, for an adequate period of time and at the lowest costs to them and to the community (6). A number of indicators have been recommended by the WHO to assess the extent of inappropriate drug use in a practice, a region or a country (7). Although crude, these indicators are easily monitored and may be used to identify particular drug-use issues that may need more detailed examination.

WHO indicators to quantify the impact of an essential drugs programme include the percentage of drugs prescribed from the EML or a formulary. However, this indicator does not take into account the volume of drugs used, and is not based on the internationally accepted measurement unit of utilization, the Defined Daily Dose (DDD) (8).

Study conducted by Björn Wettermark, Department of Clinical Pharmacology, Karolinska Institute, WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services, Stockholm, Sweden; Vera Vlahovic-Palcevski, Department of Clinical Pharmacology, University Hospital Rijeka, Croatia; Dr Richard Laing, Department of Medicines Policy and Standards, World Health Organization, Geneva, Switzerland; Ulf Bergman, Department of Clinical Pharmacology, Karolinska Institute, WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services, Stockholm, Sweden. Correspondence to: bjorn.wettermark@sll.se
The Drug Utilization 90% (DU90%) method describes patterns of drug utilization. It was originally developed with the aim to make aggregated drug statistics on dispensed drugs useful for quality assessment (8–10). DU90% is a further development of a “top 10” list providing both quantitative and qualitative data. The focus is on the drugs that account for 90% of the volume and adherence to guidelines within this 90% (8–10). The DU90% method has proven to be useful both for international comparisons of drug utilization and feedback to doctors on prescribing patterns (10–16). It can be applied with aggregated data easily available in healthcare systems. The DU90% method can also be considered as a further development of the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) methodology, recommended by WHO as a common language for describing the use of drugs — therapeutic intensity — in a population (8,17).

The study evaluated the feasibility of using the DU90%-method to assess the quality of drug use in two European countries using the 2003 EML as a reference (4).

**Methods**

The overall quality of outpatient drug use was evaluated in Croatia and Sweden, two European countries with comparable access to drug utilization data but with substantial differences in GDP and pharmaceutical markets, e.g., different number of drugs available and different healthcare organization. Basic facts about the countries are presented in Table 1.

Data on dispensed prescription and OTC drugs were collected for the year 2003. The Croatian data were captured from the wholesalers, while the Swedish data were obtained from prescriptions and OTC sales from the National Corporation of Pharmacies which has the sole and exclusive right to retail medicines to the general public and to hospitals.

Drug use was expressed in Defined Daily Doses (DDDs) and expenditure in Euros. Total drug consumption was measured using DDDs per 1000 inhabitants daily (DDD/TID). A number of drugs (231 in Croatia and 359 in Sweden) did not have assigned DDDs and therefore had to be excluded. These included dermatological preparations, nasal solutions, ophthalmic drops, cytotoxics, vaccines and some combination products.

Patterns of drug use were analysed focusing on medicines accounting for 90% of use (DU90%) in DDDs and, within this segment, adherence to the 13th WHO Model List of Essential Medicines issued in 2003 (4). The core list presents a minimum medicine need for a basic health care system listing the most efficacious, safe and cost-effective medicines for priority conditions. The complementary list presents essential medicines for priority diseases, for which specialized diagnostic/monitoring and medical care/training are needed. Medicines marked with a square symbol are those with similar clinical performance within a pharmacological class (“me-too” drugs). Both the core and complementary list with 316 drugs were used for this analysis.

DU90% profiles were analysed for all drugs (ATC A–V) and for the seven ATC pharmacological groups with high utilization, reflecting major disease patterns in the two countries Tables 2 and 3.

**Table 1. Facts about Croatia and Sweden 2002**

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Croatia</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>4.4 million</td>
<td>8.9 million</td>
</tr>
<tr>
<td>Percentage of population aged 60+</td>
<td>21.7 %</td>
<td>23.2 %</td>
</tr>
<tr>
<td>GDP per capita</td>
<td>$8,636.-</td>
<td>$27,271.-</td>
</tr>
<tr>
<td>Health expenditure per capita</td>
<td>$630.-</td>
<td>$2,512.-</td>
</tr>
<tr>
<td>Health expenditure % of GDP</td>
<td>7.3 %</td>
<td>9.3 %</td>
</tr>
</tbody>
</table>
Table 2. Drug utilization within selected therapeutic areas: Croatia and Sweden

<table>
<thead>
<tr>
<th>ATC Pharmacological group</th>
<th>Croatia</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DDD/TID</td>
<td>Adherence</td>
</tr>
<tr>
<td></td>
<td>Number of Drugs</td>
<td>1*</td>
</tr>
<tr>
<td>A02 Drugs: acid related disorders</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>A10 Antidiabetic drugs</td>
<td>34</td>
<td>11</td>
</tr>
<tr>
<td>C Cardiovascular drugs</td>
<td>214</td>
<td>52</td>
</tr>
<tr>
<td>J01 Antibiotics</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>M01A NSAIDs</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td>N06A Antidepressants</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>R Respiratory drugs</td>
<td>45</td>
<td>30</td>
</tr>
</tbody>
</table>

*1* = Adherence to the core list within DU90%.

*2* = Adherence within DU90% including alternatives to drugs marked with a square symbol in the EML.

Table 3. Most used drugs in Croatia and Sweden in percent of total use within each pharmacological group. Utilization in DDDs.

<table>
<thead>
<tr>
<th>ATC Pharmacological group</th>
<th>Croatia</th>
<th>Sweden</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>A02 Drugs for acid related disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine (46%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lansoprazole (29%)</td>
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</tr>
<tr>
<td>Pantooprazole (20%)</td>
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<td></td>
</tr>
<tr>
<td>Omeprazole (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aluminium hydroxide (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A10 Antidiabetic drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glibenclamide (35%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin (22%)</td>
<td></td>
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</tr>
<tr>
<td>Insulin (human), fast-acting (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gliclazide (7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C Cardiovascular drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol (7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J01 Antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin + clavulanic acid (28%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycycline (28%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenoxyemethylpenicillin (28%)</td>
<td></td>
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</tr>
<tr>
<td>J01 Antibiotics</td>
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<td></td>
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<tr>
<td>Doxycycline (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methenamine (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flucloxacinil (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M01A NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac (55%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piroxicam (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoprofen (10%)</td>
<td></td>
<td></td>
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<tr>
<td>N06A Antidepressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine (29%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (24%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline (19%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maprotiline (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Respiratory drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loratadine (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salbutamol (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxymetazole (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naphazoline (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxymetazoline (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xylometazoline (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terbutaline (7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Italic = Included in Model list of Essential Medicines (EML). ■ = Alternative drugs, marked with a square symbol in EML.*

Results

Total utilization was 682 DDD/TID in Croatia compared to 1360 in Sweden. In Croatia 95 substances (24% of 388) accounted for 90% of use compared to 174 (21% of 828) in Sweden. Drug profiles had many similarities in the two countries with high use of drugs for treatment of cardiovascular disease, diabetes, pain and psychiatric disorders. (Figures 1A and 1B).
Adherence to the EML within DU90% was 40% in Croatia and 37% in Sweden. Low adherence in both countries was partly due to the utilization of “me-too” drugs different to those included in the EML. When adding the medicines suggested as alternatives to those recommended in the EML (square symbols), adherence increased to 73% and 53%, respectively. There were also some drugs extensively used in both countries that were not included in the EML (e.g. proton pump inhibitors (PPIs), serotonin selective reuptake inhibitors).

Figure 1A. DU90% profile for Croatia 2003 — outpatient care

```
<table>
<thead>
<tr>
<th>SUBSTANCE</th>
<th>(DDD)</th>
<th>Mill. DDD</th>
<th>% TOT</th>
<th>Mill Euro</th>
<th>Euro/DDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>2 mg</td>
<td>85</td>
<td>7.7%</td>
<td>1.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>1 tabl</td>
<td>84</td>
<td>7.7%</td>
<td>2.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10 mg</td>
<td>45</td>
<td>4.1%</td>
<td>12.3</td>
<td>0.27</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>5 mg</td>
<td>39</td>
<td>3.6%</td>
<td>10.0</td>
<td>0.25</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>0.1 g</td>
<td>36</td>
<td>3.3%</td>
<td>6.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Ascorbic acid (vit C)</td>
<td>0.2 g</td>
<td>35</td>
<td>3.2%</td>
<td>1.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
<td>34</td>
<td>3.1%</td>
<td>1.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Diazepam</td>
<td>10 mg</td>
<td>31</td>
<td>2.8%</td>
<td>3.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Atenolol</td>
<td>75 mg</td>
<td>25</td>
<td>2.3%</td>
<td>3.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>15 mg</td>
<td>24</td>
<td>2.2%</td>
<td>16.2</td>
<td>0.67</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>40 mg</td>
<td>22</td>
<td>2.0%</td>
<td>4.0</td>
<td>0.19</td>
</tr>
<tr>
<td>Levothryoxine</td>
<td>0.15 mg</td>
<td>21</td>
<td>1.9%</td>
<td>0.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>50 mg</td>
<td>19</td>
<td>1.7%</td>
<td>4.4</td>
<td>0.23</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>7 mg</td>
<td>19</td>
<td>1.7%</td>
<td>1.8</td>
<td>0.09</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>1 mg</td>
<td>16</td>
<td>1.5%</td>
<td>2.5</td>
<td>0.16</td>
</tr>
<tr>
<td>Verapamil</td>
<td>0.24 g</td>
<td>15</td>
<td>1.3%</td>
<td>2.5</td>
<td>0.17</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>2.5 mg</td>
<td>13</td>
<td>1.2%</td>
<td>4.3</td>
<td>0.34</td>
</tr>
<tr>
<td>Loratadine</td>
<td>10 mg</td>
<td>12</td>
<td>1.1%</td>
<td>3.3</td>
<td>0.27</td>
</tr>
<tr>
<td>Metildigoxin</td>
<td>0.2 mg</td>
<td>11</td>
<td>1.0%</td>
<td>0.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Chlortalidone</td>
<td>25 mg</td>
<td>11</td>
<td>1.0%</td>
<td>0.8</td>
<td>0.07</td>
</tr>
</tbody>
</table>
```

Green = medicines included in the core EML. Yellow = alternatives to medicines, i.e. those marked with a box symbol in the EML. Red = medicines not on the EML.
inhibitors (SSRIs) and statins). Including them, adherence would have been 78% in Croatia and 64% in Sweden.

There were substantial differences between the two countries in the total utilization (DDD/TID), the range of drugs and adherence within the selected therapeutic areas (Tables 2 and 3).

Discussion
Drug utilization was twice as high in Sweden as in Croatia. In addition, different drugs were used in Sweden than in Croatia, both totally and in the selected therapeutic areas (Table 3). These cannot be explained by differences in morbidity but rather by differences in GNP per capita and therapeutic traditions. It has been suggested that high-quality prescribing is
associated with the use of a relatively limited number of evidence-based documented pharmaceutical products (19). The relationship between the range of drugs and quality has been demonstrated for individual prescribers (20). It is not obvious what impact the range of different drugs prescribed in a region or a country may have on public health. A reasonable distribution among the major ATC groups can be expected. A lack of products in certain ATC categories, as well as too many products in other categories, may indicate quality problems. The high number of “me-too” drugs used in Sweden is probably explained by the higher GNP/capita and through EU membership increasing the availability of drugs on the market.

How many medicines cover the needs of a population? In our study, 95 substances (of 388) accounted for 90% of outpatient use in Croatia compared with 174 (of 828) in Sweden. The Essential Medicines List includes 316 drugs. However, the selection of medicines reflects the global need, including drugs for hospital care and many drugs for the treatment of infectious diseases not prevalent in a European population.

Low adherence to the EML in both countries was mainly explained by the use of “me-too” drugs and newer drugs not included in the 2003 EML (PPIs, SSRIs and statins). These medicines were highly used in both countries. It has been shown that they offer advantages over older therapies (21–24). The study therefore also raises questions concerning the relevance of the WHO EML. It seems that the EML may be more relevant for developing countries where the overall adherence is reported to be much higher. Although different methods (prescription audits) were used, adherence to WHO EML in Jordan primary care was reported to be 93% (25), while similar studies from Bangladesh, Nepal and Tanzania reported 85% and 88% (7). However, the absence of PPI’s, SSRI’s and statins reflect a serious problem in the comprehensive nature of the WHO EML. These products are widely used in developed countries.

Comparison of the profiles for the selected pharmacological groups revealed interesting differences between the two countries (Table 2). Utilization of drugs for acid related disorders was almost three times higher in Sweden than Croatia. The three most used drugs for acid related disorders in Sweden were all proton pump inhibitors (PPIs) while ranitidine was the most used drug followed by two PPIs in Croatia. Half of the PPI volume in Sweden was prescribed to patients with unspecified dyspepsia: which is not according to treatment guidelines (26).

The overall utilization and adherence in diabetic treatment was similar. However, metformin was used to a greater extent in Sweden, which is in accordance with findings from the UK Prospective Diabetes Study that metformin decreases mortality and morbidity (27).

Low adherence for cardiovascular drugs in both countries was mainly explained by a high utilization of “me-too” drugs. Some examples were lisinopril, ramipril and amlodipine instead of the EML drugs enalapril and nifedipine. Adherence rose substantially when including alternatives to medicines marked with a square symbol.

No statin is included in the EML. However, it is stated in the EML that since no single drug has been shown to be significantly more effective or less expensive, the choice of drug should be decided on a national level (28). Simvastatin is well documented, and it had a lower price than other statins in both countries due to an expired patent at the time of the study. It should therefore be considered as the drug of choice to be included on the EML.

As reported for other European countries, there were striking differences in the utilization of antibiotics (29). It was the only therapeutic area where utilization was higher in Croatia than in Sweden. The most commonly used antibiotic in Croatia was amoxicillin in fixed combination with clavulanic acid. Although included in the EML, it is not a first choice medicine for the empiric treatment of upper respiratory tract infections, the most commonly treated (often viral!) infections in primary care. The most used antibiotic in Sweden was phenoxymethylpenicillin, a more reasonable choice with regard to the development of resistance and price. In Croatia, antibiotics were the drug group with the highest adherence to the EML — which does not imply that they are the most rationally used drug group.
Total utilization of NSAIDs was similar, but the range of medicines differed between countries. Overall utilization had increased but the choice of drugs was similar to that observed in 2000 (12). The two most extensively used drugs were ibuprofen and diclofenac in both countries. Questions could be raised about the high use of piroxicam in Croatia and coxibs in Sweden. Ibuprofen was the only NSAID included in the EML. It could be worth adding diclofenac to the EML since it is at least as effective as ibuprofen and has a similar safety profile (30).

Utilization of antidepressants was six times higher in Sweden. This might reflect a higher prevalence of depression, differences in access to healthcare or differences in treatment practices. Most used antidepressants in both countries were SSRIs, but the newer SNRIs, venlafaxine and mirtazapine were only used in Sweden. We propose that an SSRI is added to the WHO Model list since these drugs appear to have fewer side effects than tricyclic antidepressants (23).

The low adherence for respiratory drugs in both countries was mainly explained by the use of newer, less sedating antihistamines instead of chlorphenamine and high use of budesonide, fluticasone and terbutaline instead of the recommended beclometasone and salbutamol, respectively. There was also a high use of nasal decongestants and cough suppressants in both countries. There were no alternative drugs to those included in the WHO Model List.

A new version of the EML has been issued since this study was performed (31). Some newer drugs have been included though not a PPI, an SSRI or a specific statin. However, to make the list more relevant, we propose that at least the complementary list includes a statin, a PPI, a SSRI, a new nonsedating antihistamine and diclofenac. We also suggest that a revision of the square symbols should be undertaken. Results from both countries have shown that the EML, if it included suggested drugs, would be closer to its initial mission of covering the necessary treatment options for the majority of the world’s population.

In an ideal world, “rationality” should be determined by looking at patient outcomes, i.e. does the treatment succeed in reducing morbidity and mortality and increasing patient quality of life. However, it is seldom possible to analyse patient outcome with routinely available data, and the outcome is only partially influenced by the processes controlled by healthcare professionals. Therefore, process-oriented quality indicators are used to monitor the performance of healthcare systems.

The advantage of DU90% compared to the drug-use indicators recommended by WHO is that it takes into account the volume of used drugs, utilizes easily collectible data and is based the ATC–DDD methodology that facilitates international comparisons. This study has confirmed that the DU90% method is simple, inexpensive, understandable and easy to use for quality assessment. Comparison with the EML may be useful for decision-making (e.g., preparing national formularies). The DU90% profiles provide a quick overview of potential improvements in both studied countries but are also a reflection on the relevance and appropriateness of the WHO Essential Medicines List.

References


**Regulatory Action and News**

### Transgenic antithrombin alfa approved

**European Union** — The European Medicines Agency (EMEA) has adopted the first positive opinion for a medicinal product derived from transgenic biotechnology. ATryn®, contains antithrombin alfa, a recombinant-DNA human anti-clotting blood protein. Antithrombin alfa is extracted from the milk of goats which have the human antithrombin gene inserted, and that enables them to produce the human protein in their milk.

The Agency’s Committee for Medicinal Products for Human Use (CHMP) recommended that ATryn® should be authorized for use in patients with congenital antithrombin (AT) deficiency (inherited reduction of antithrombin) undergoing surgery, for the prophylaxis of deep-vein thrombosis and thromboembolism.

In February 2006, ATryn® received a negative opinion. At the request of the company, the Committee started a procedure to re-examine its opinion, as part of which further expert advice was obtained. The CHMP has concluded that the benefits of ATryn® outweigh its risks, and subsequently adopted a final positive opinion recommending that ATryn® be granted a marketing authorization.


### Bupropion approved for seasonal depression

**United States of America** — The Food and Drug Administration (FDA) today approved bupropion HCL extended release tablets (Wellbutrin XL®) for prevention of major depressive episodes in patients with a history of seasonal affective disorder (SAD). This is the first drug approved for SAD. Bupropion has been approved for treatment of major depressive disorder.

SAD is characterized by recurrent major depressive episodes that usually coincide with the seasonal decrease of daylight during autumn and winter. Depressive episodes can last up to 6 months. Although patients with SAD may have depressive episodes during other times of the year, the diagnosis of seasonal affective disorder requires that the number of seasonal episodes substantially outnumber the non-seasonal episodes during the individual’s lifetime.

A major depressive episode is defined as the presence of 5 or more of the 9 core symptoms of major depression for at least 2 weeks. The symptoms include: depressed mood; loss of interest; weight loss (or other weight or appetite changes); insomnia or hypersomnia; agitation or psychomotor retardation; fatigue; feelings of worthlessness or guilt; impaired concentration; suicidal thinking or behaviour. One of the 5 symptoms must be either


### EMEA Management Board moves for greater transparency

**European Union** — Transparency was the main topic for discussion of the European Medicines Agency’s Management Board at its 8 June 2006 meeting. The Board agreed in principle to publish its meeting agendas and minutes, together with all non-confidential documents it adopts. Details will be set out in a policy document to be presented at the next Board meeting on 28 September 2006.

The Board also adopted revised rules on access to EMEA documents. Following this revision, the Agency’s rules better reflect European Union legislation on access to documents, and the types of documents that can be released have been clarified. The rules also introduce the possibility for the Agency to give partial access to documents when exceptions to release apply to other parts of the document.

depressed mood or loss of interest in activities. Another essential feature of major depression is the presence of significant distress or impairment in social, occupational, or other important areas of functioning. A seasonal major depressive episode is defined by the identical features.

Labelling includes a “black box” warning concerning the increased risk of suicidal thoughts and behaviour in paediatric patients treated with antidepressant medications.


Decitabine approved for myelodysplastic syndromes

United States of America — The Food and Drug Administration (FDA) has approved decitabine (Dacogen) injection for the treatment of myelodysplastic syndromes (MDS). Dacogen is a new molecular entity that has received orphan drug status.

Decitabine is thought to work by promoting normal development of blood cells. Different types of MDS exist, resulting in different manifestations of the disease. MDS can develop following treatment with drugs or radiation therapy for other diseases or it can develop without any known cause. Some forms of MDS can progress to acute myeloid leukaemia (AML), a type of cancer in which too many white blood cells are made.

An estimated 7000 to 12 000 new cases of MDS are diagnosed yearly in the United States. Although MDS occurs in all age groups, the highest prevalence is in people over 60 years of age. Typical symptoms include weakness, fatigue, infections, easy bruising, bleeding, and fever.

The most common side effects reported in clinical trials included neutropenia (low white blood cell count), thrombocytopenia (low platelets in blood), anaemia, fatigue, fever, nausea, cough, bleeding in the skin, constipation, diarrhoea, and hyperglycaemia (high blood sugar).


Medical device innovation initiative

United States of America — The Food and Drug Administration (FDA) is launching the Medical Device Innovation Initiative to make new medical devices available more quickly for patients. This broad initiative will promote early interaction between the FDA and industry to optimize review times and foster innovation.

With the convergence of many scientific and technology breakthroughs, the pace of medical invention is accelerating, inspiring hope for better health outcomes with less invasive procedures and shorter recovery times. As part of this initiative, new guidelines provide recommendations on the use of Bayesian statistical methods in the design and analysis of medical device clinical trials. The use of Bayesian statistics offers industry the option of using prior, legally available information about safety and/or effectiveness in a mathematically acceptable way to design more efficient clinical trials, while still maintaining scientific rigor.


Topotecan/cisplatin for late-stage cervical cancer

United States of America — The Food and Drug Administration (FDA) has approved a combination of topotecan hydrochloride (Hycamtin®) and cisplatin for use as the first drug treatment for women with late-stage cancer of the cervix when a physician determines that surgery or radiation therapy are unlikely to be effective. The approval includes a new indication for topotecan, which was approved in 1996 for treating ovarian cancer and in 1998 for small cell lung cancer.

The combination of topotecan and cisplatin is specifically indicated for women with Stage IVB (incurable), recurrent, or persistent cancer of the cervix which spreads to other organs and is not likely to respond to treatment with surgery or radiation.

In clinical trials, the combination significantly improved survival compared to the use of cisplatin alone. Patients on combined therapy survived about three months longer than patients on cisplatin alone.
Topotecan is associated with a significant risk of neutropenia, a condition which makes it more difficult for the body to fight infections. Serious side effects also include thrombocytopenia, a decrease in blood platelets that can lead to excessive bleeding and anaemia. Less serious side effects include nausea and vomiting. The incidences of neutropenia, anaemia, and thrombocytopenia were significantly increased among patients receiving the combination treatment compared to those receiving cisplatin alone, as were nausea and vomiting, mucositis, rash, and liver toxicity.


Rapid approval of vaccine for prevention of cervical cancer

United States of America — The Food and Drug Administration (FDA) has announced the approval the first vaccine developed to prevent cervical cancer, precancerous genital lesions and genital warts due to human papillomavirus (HPV). The vaccine is approved for use in females 9–26 years of age. Gardasil® was evaluated and approved in six months under FDA’s priority review process—a process for products with potential to provide significant health benefits.

HPV is the most common sexually-transmitted infection in the United States. Worldwide, cervical cancer is the second most common cancer in women, and is estimated to cause over 470,000 new cases and 233,000 deaths each year.

For most women, the body’s own defence system will clear the virus and infected women do not develop related health problems. However, some HPV types can cause abnormal cells on the lining of the cervix that years later can turn into cancer. Other HPV types can cause genital warts. The vaccine is effective against HPV types 16 and 18, which cause approximately 70 percent of cervical cancers and against HPV types 6 and 11, which cause approximately 90 percent of genital warts.

Gardasil® is a recombinant vaccine that is given as three injections over a six-month period. Immunization is expected to prevent most cases of cervical cancer due to HPV types included in the vaccine. However, females are not protected if they have been infected prior to vaccination, indicating the importance of immunization before potential exposure to the virus. Also, Gardasil® does not protect against less common HPV types not included in the vaccine, thus routine and regular pap screening remain critically important to detect precancerous changes in the cervix to allow treatment before cervical cancer develops.

The safety of the vaccine was evaluated in approximately 11,000 individuals. Most adverse experiences included mild or moderate local reactions, such as pain or tenderness at the site of injection. The manufacturer has agreed to conduct several studies following licensing, including additional studies to further evaluate general safety and long-term effectiveness. The manufacturer will also monitor the pregnancy outcomes of women who receive Gardasil® while unknowingly pregnant. Also, the manufacturer has an ongoing study to evaluate the safety and effectiveness in males.


Rasagiline approved for Parkinson disease

United States of America — The Food and Drug Administration has approved rasagiline (Azilect®), a new molecular entity, for the treatment of Parkinson disease. The drug is a monoamine oxidase type—B (MAO-B) inhibitor that blocks the breakdown of dopamine.

Rasagiline was approved for use as an initial single drug therapy in early Parkinson disease, and as an addition to levodopa in more advanced patients. Rasagiline may be associated with hypertensive crisis if patients also consume tyramine-rich foods and beverages (such as cheese and red wine) or dietary supplements or amines contained in many cough/cold medications. Therefore, patients will need to avoid these sources of tyramine and amines when taking rasagiline. As with many other medications for Parkinson, rasagiline has the potential to cause dyskine-
sias, hallucinations and lowered blood pressure. These side effects are described in the product labelling.

During development, melanoma was diagnosed in a small number of patients treated with rasagiline. Although the FDA has concluded that the available data do not establish that Azilect® is associated with an increased risk for melanoma, it appears that compared to the general population, patients with Parkinson disease have an increased risk for this form of skin cancer. The drug’s manufacturer will perform a Phase IV postmarket study and the product labelling will recommend that patients undergo periodic dermatologic examinations.

Reference: FDA News, P06-68. 17 May 2006

Fluoxetine approved for children and adolescents

European Union — The European Medicines Agency (EMEA) has recommended to extend the indication for fluoxetine (Prozac®) and associated names to include the treatment of children of 8 years of age or older who suffer from moderate to severe depression and who do not respond to psychological therapy. The Agency’s Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of using fluoxetine in this indication outweigh its potential risks, but that the marketing authorization holder (MAH), should carry out additional studies to ensure that the safety profile of fluoxetine remains acceptable.

Prozac® and associated names is authorized in most EU Member States for the treatment of major depressive episodes, obsessive-compulsive disorder and bulimia nervosa in adults.

Based on the data, the CHMP concluded:

• The starting dose should be 10 mg per day (given as 2.5 ml of oral solution) and may be increased to 20 mg per day after one to two weeks.

• If no clinical benefit is seen within 9 weeks, treatment should be reconsidered.

• The significance of the observations in animal studies on sexual development, emotional behaviour and testicular toxicity will be further investigated. The MAH will also put in place a system to obtain safety data in treated children, in particular regarding sexual development.

• The CHMP confirmed that doctors and parents should carefully monitor children and adolescents for suicidal behaviour, particularly at the beginning of treatment.


Withdrawal of marketing application for Surfaxin®

European Union — The European Medicines Agency has been formally notified by the manufacturer of the orphan medicinal product Surfaxin® of their decision to withdraw the application for a centralized marketing authorization. The active substances of Surfaxin® are sinapultide, dipalmitoyl-phosphatidylcholine, palmitoyloleoyl phosphatidylglycerol and palmitic acid for the prevention and treatment of respiratory distress syndrome in premature babies.

At the time of the withdrawal, the application was under review by the Committee for Medicinal Products for Human Use (CHMP). In its official withdrawal letter, the company stated that the withdrawal was due to manufacturing and clinical issues. More information about Surfaxin® and the current state of the scientific assessment at the time of withdrawal will be made available in a question and answer document to be published on the EMEA website at http://www.emea.eu.int.
Resumed marketing of natalizumab

United States of America — The Food and Drug Administration (FDA) has approved an application for resumed marketing of natalizumab (Tysabri®) subject to a special restricted distribution programme. Natalizumab is a monoclonal antibody used to treat patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of exacerbations (flare-ups). Natalizumab is indicated for use as monotherapy since its use with other immune modifying drugs could impact risk. It is also meant for patients who have not responded adequately to, or cannot tolerate, other treatments for MS.

Tysabri® was initially approved by the FDA in November 2004, but was withdrawn by the manufacturer in February 2005 after three patients in the drug's clinical trials developed progressive multifocal leukoencephalopathy (PML), a serious and rare viral infection of the brain. Two of the cases were fatal. Based on this information, FDA put clinical trials of the drug on hold in February 2005. FDA allowed a clinical trial to resume in February 2006, following a re-examination of the patients who had participated in the previous clinical trials, confirming that there were no additional cases of PML.

The Peripheral and Central Nervous Systems Drugs Advisory Committee recommended a risk-minimization programme with mandatory patient registration and periodic follow-up. Natalizumab will only be prescribed, distributed, and infused by prescribers, infusion centres, and pharmacies registered with the programme.

Reference: FDA News, P06-75. 6 June 2006

EU Regulation on compulsory licensing published

The European Union regulation text on compulsory licensing of patents relating to the manufacture of pharmaceutical products for export to countries with public health problems was published in the Official Journal of the EU on 9 June 2006. It entered into force on the twentieth day following that of its publication in the EU Official Journal, i.e., 29 June 2006.

Emerging Diseases

Tissue infectivity and transmissible spongiform encephalopathies

A variant form of a fatal brain disease, Creutzfeldt-Jakob disease (vCJD), was first identified in the mid-1990s as a result of suspected bovine spongiform encephalopathy (BSE) transmission to humans in the United Kingdom. Since then, cases of vCJD have occurred in Canada, France, Ireland, Italy, Japan, Netherlands, Portugal, Saudi Arabia, Spain, USA, and the United Kingdom.

Until recently, all vCJD cases were attributed to consumption of beef products contaminated with the infectious agent of BSE. However, since December 2003, three individuals have been identified with vCJD infections probably acquired from blood transfusions. The fact that the three vCJD infections followed transfusions from clinically healthy persons who became ill more than a year after donating blood implies that other blood donors who might currently be incubating the disease could also be potential sources of infection. The possible extent of future blood-borne spread of vCJD infections is still unknown. The identification of these cases has intensified the concern about possible unmapped ways in which the disease might spread. Except for the three transfusion-transmitted infections, no cases of vCJD have been linked to any medicinal product to date, and guidelines have been developed by the World Health Organization (WHO) and other authorities to minimize the risk (1).

A consultation held at WHO in September 2005 brought together experts and regulators from around the world to revise existing WHO Guidelines on Transmissible Spongiform Encephalopathies (TSEs) in relation to Biological and Pharmaceutical Products (2) which recommended ways to prevent potential transmission of vCJD through human blood and blood products, or medicinal products prepared with bovine derived materials. The primary objective of the Consultation was to provide evidence-based information to national regulatory authorities to assist in conducting risk assessments and selecting measures to reduce the risk of transmitting vCJD through human blood and blood products and other medicinal products of biological origin. These and other issues discussed during the consultation have now been published as WHO Guidelines on tissue infectivity distribution in transmissible spongiform encephalopathies and are available on the WHO website (3). The Guidelines ensure that all national regulatory authorities with limited resources have ready access to reliable and up-to-date information when assessing TSE risks and evaluating product safety.

WHO consultations have repeatedly encouraged authorities to consider introducing precautionary measures to minimize possible risks to blood and blood products while not compromising supply and have stressed that tissues or body fluids of ruminant origin should be avoided in the preparation of biological and pharmaceutical products. When bovine materials must be used, they should be obtained from sources assessed to have negligible risk from the infectious agent of BSE. Most bovine tissues and bovine muscle used to manufacture biologicals have little risk of contamination with BSE agent if carefully selected and collected according to guidelines.

Bovine blood has not been identified as a source of infection, and properly collected fetal bovine serum has a negligible risk. However, the blood of sheep with experimental BSE or natural scrapie can be infectious and, because scrapie and BSE agents behave similarly in sheep and goats, the blood of small ruminants should either be avoided in preparing biologicals or selected very carefully from sources known to be free of TSEs.

Current knowledge concerning major categories of infectivity is set out on the following pages.
**Major categories of infectivity tables**

The information set out in the following tables is based exclusively upon observations of naturally occurring disease, or primary experimental infection by the oral route in ruminants, and does not include data on models using strains of transmissible spongiform encephalopathy (TSE) adapted to experimental animals, because passaged strain phenotypes can differ significantly and unpredictably from those of naturally occurring disease. Also, because detection of misfolded host prion protein \( (\text{Pr}^{\text{PTSE}}) \) has proven to be a reliable indicator of infectivity, \( \text{Pr}^{\text{PTSE}} \) testing results have been presented in parallel with bioassay data. Tissues are grouped into three major infectivity categories, irrespective of the stage of disease:

A: High-infectivity tissues: central nervous system (CNS) tissues that attain a high titre of infectivity in the later stages of all TSEs, and certain tissues that are anatomically associated with the CNS.

B: Lower-infectivity tissues: peripheral tissues that have tested positive for infectivity and/or \( \text{Pr}^{\text{PTSE}} \) in at least one form of TSE.

C: Tissues with no detectable infectivity: tissues that have been examined for infectivity and/or \( \text{Pr}^{\text{PTSE}} \) with negative results.

Data entries are shown as follows:

- Presence of infectivity or \( \text{Pr}^{\text{PTSE}} \)
- Absence of detectable infectivity or \( \text{Pr}^{\text{PTSE}} \)
- Not tested
- Not applicable
- Controversial results
- Limited or preliminary data

The placement of a given tissue in one or another category can be disease-specific and subject to revision as new data accumulate from increasingly sensitive tests. In fact, it is conceivable that the detection of infectivity using transgenic mice that over-express genes encoding various prion proteins, or the detection of \( \text{Pr}^{\text{PTSE}} \) using some newly developed amplification methods, might prove to be more sensitive than transmission studies in wild-type bioassay animals, and thus may not correlate with disease transmission in nature.

It is also important to understand that categories of infectivity are not the same as categories of risk, which require consideration not only of the level of infectivity in tissue, but also of the amount of tissue to which a person or animal is exposed, and the route by which infection is transmitted. For example, although the level of tissue infectivity (concentration of infectivity in tissue as reflected by titre) is the most important factor in estimating the risk of transmission by instrument cross contamination during surgical procedures (e.g., neurosurgery versus general surgery), it is only one determinant of the risk of transmission by blood transfusions, in which a large amount of low-infectivity material is administered directly into the circulation, or the risk of transmission by food that, irrespective of high or low infectivity, involves the comparatively inefficient oral route of infection.
**Table A: High-infectivity tissues**

<table>
<thead>
<tr>
<th>Tissues</th>
<th>Human TSEs</th>
<th>Cattle</th>
<th>Sheep &amp; goats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vCJD Infectivity&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Other TSEs Infectivity&lt;sup&gt;1&lt;/sup&gt;</td>
<td>BSE</td>
</tr>
<tr>
<td>Cognate tissues that attain a high titre of infectivity in the later stages of TSE and certain tissues anatomically associated with the CNS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Retina</td>
<td>NT</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Optic nerve&lt;sup&gt;2&lt;/sup&gt;</td>
<td>NT</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>Spinal ganglia</td>
<td>+</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>Trigeminal ganglia</td>
<td>+</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>Pituitary gland&lt;sup&gt;3&lt;/sup&gt;</td>
<td>NT</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>Dura mater&lt;sup&gt;3&lt;/sup&gt;</td>
<td>NT</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

**Footnotes:**

1. Infectivity bioassays of human tissues have been conducted in either primates or mice (or both); bioassays of cattle tissues have been conducted in either cattle or mice (or both); and most bioassays of sheep and/or goat tissues have been conducted only in mice. In regard to sheep and goats, not all results are consistent for both species.

2. In experimental models of TSE, the optic nerve has been shown to be a route of neuroinvasion and contains high titres of infectivity.

3. No experimental data about infectivity in human pituitary gland or dura mater have been reported, but cadaveric dura mater allograft patches, and growth hormone derived from cadaveric pituitaries have transmitted disease to hundreds of people and therefore must be included in the category of high-risk tissues.

**Table B: Lower-infectivity tissues**

<table>
<thead>
<tr>
<th>Tissues</th>
<th>Human TSEs</th>
<th>Cattle</th>
<th>Sheep &amp; goats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vCJD Infectivity&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Other TSEs Infectivity&lt;sup&gt;1&lt;/sup&gt;</td>
<td>BSE</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>+</td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>Peripheral nerves</td>
<td>NT</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>Enteric plexuses&lt;sup&gt;4&lt;/sup&gt;</td>
<td>NT</td>
<td>-</td>
<td>NT</td>
</tr>
</tbody>
</table>

.../...
### Table B: Lower-infectivity tissues (continued)

Peripheral tissues that have tested positive for infectivity and/or PrP^TSE in at least one form of TSE

<table>
<thead>
<tr>
<th>Tissues</th>
<th>Human TSEs</th>
<th>Cattle</th>
<th>Sheep &amp; goats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vCJD</td>
<td>Other TSEs</td>
<td>BSE</td>
</tr>
<tr>
<td></td>
<td>Infectivity</td>
<td>PrP^TSE</td>
<td>Infectivity</td>
</tr>
<tr>
<td>Lymphoreticular tissues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tonsil</td>
<td>+</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>Nictitating membrane</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Thymus</td>
<td>NT</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>Alimentary tract</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>NT</td>
<td>-</td>
<td>NT</td>
</tr>
<tr>
<td>Fore-stomach (ruminants only)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Stomach/abomasum</td>
<td>NT</td>
<td>-</td>
<td>NT</td>
</tr>
<tr>
<td>Duodenum</td>
<td>NT</td>
<td>-</td>
<td>NT</td>
</tr>
<tr>
<td>Jejunum</td>
<td>NT</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>Ileum</td>
<td>NT</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>Appendix</td>
<td>-</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>Large</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive tissues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placenta</td>
<td>NT</td>
<td>-</td>
<td>(+)</td>
</tr>
<tr>
<td>Other tissues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>NT</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Liver</td>
<td>NT</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Kidney</td>
<td>NT</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Adrenal</td>
<td>NT</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Pancreas</td>
<td>NT</td>
<td>-</td>
<td>NT</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>NT</td>
<td>-</td>
<td>NT</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>NT</td>
<td>+</td>
<td>(-)</td>
</tr>
<tr>
<td>Tongue</td>
<td>NT</td>
<td>-</td>
<td>NT</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>NT</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>Nasal mucosa</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Cornea</td>
<td>NT</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Body fluids</td>
<td>NT</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CSF</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

**Footnotes:**

4. In cattle, PrP^TSE was limited to enteric plexus in the distal ileum.
5. Ruminant fore-stomachs (reticulum, rumen, and omasum) are widely consumed, as is the true stomach (abomasum). The abomasum of cattle (and sometimes sheep) is also a source of rennet.
6. In vCJD, transmission to mice has so far been limited to rectal tissue, and PrP^TSE was detected only in gut-associated lymphoid and nervous tissue (mucosa, muscle, and serosa were negative). In goats, PrP^TSE was also limited to gut-associated lymphoid and nervous tissue [Andreoletti, unpublished data]
7. In cattle and sheep, only the distal ileum has been bioassayed for infectivity.
8. A single report of transmission of CJD infectivity from human placenta has never been confirmed and is considered improbable.
9. Muscle homogenates have not transmitted disease to primates from humans with sCJD, or to cattle from cattle with BSE. However, intracerebral inoculation of a semitendinosus muscle homogenate (including nervous and lymphatic elements) from a single cow with BSE has transmitted disease to PrP-over-expressing transgenic mice at a rate indicative of only trace levels of infectivity. Also, recent published and unpublished studies have reported the presence of PrP\textsuperscript{TSE} in skeletal muscle in experimental rodent models of scrapie and vCJD, in experimental and natural infections of sheep and goats, in sheep orally dosed with BSE [Andreoletti, unpublished data], and in humans with sCJD, iCJD and vCJD. Bioassays to determine whether PrP\textsuperscript{TSE} is associated with transmissibility in these experimental or natural infections are in progress.
10. In cattle, infectivity bioassay was negative, but the presence of PrP\textsuperscript{TSE} in palatine tonsil has raised concern about possible infectivity in lingual tonsillar tissue at the base of the tongue that may not be removed at slaughter.
11. In sCJD, PrP\textsuperscript{TSE} is limited to olfactory mucosa.
12. Because only one or two cases of CJD have been plausibly attributed to corneal transplants among hundreds of thousands of recipients, cornea is categorised as a lower-risk tissue; other anterior chamber tissues (lens, aqueous humor, iris, conjunctiva) have been tested with a negative result both in vCJD and other human TSEs, and there is no epidemiological evidence that they have been associated with iatrogenic disease transmission.
13. A wealth of data from studies of blood infectivity in experimental animal models of TSE has been extended by recent studies documenting infectivity in the blood of sheep with naturally occurring scrapie, and (from epidemiological observations) three blood-associated vCJD transmissions in humans. Blood has not been shown to transmit disease from patients with any other form of TSE, or from cattle with BSE (including fetal calf blood). However, several laboratories using new, highly sensitive methods to detect PrP\textsuperscript{TSE} claim success in studies of plasma and/oruffy coat in a variety of animal and human TSEs. Because the tests are all in a preliminary stage of development (and do not yet include results on blinded testing of specimens from naturally infected humans or animals), the Consultation felt that it was still too early to evaluate the validity of these tests with sufficient confidence to permit either a negative or positive conclusion.

Table C: Tissues with no detected infectivity or PrP\textsuperscript{TSE}

<table>
<thead>
<tr>
<th>Tissues</th>
<th>Human TSEs</th>
<th>Cattle</th>
<th>Sheep &amp; goats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vCJD</td>
<td>Other TSEs</td>
<td>BSE</td>
</tr>
<tr>
<td>PrP\textsuperscript{TSE}</td>
<td>Infectivity\textsuperscript{1}</td>
<td>PrP\textsuperscript{TSE}</td>
<td>Infectivity\textsuperscript{1}</td>
</tr>
<tr>
<td>Reproductive issues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testis</td>
<td>NT</td>
<td>-</td>
<td>(-)</td>
</tr>
<tr>
<td>Prostate/ Epididymis/ Seminal vesicle</td>
<td>NT</td>
<td>-</td>
<td>(-)</td>
</tr>
<tr>
<td>Semen</td>
<td>NT</td>
<td>-</td>
<td>(-)</td>
</tr>
<tr>
<td>Ovary</td>
<td>NT</td>
<td>-</td>
<td>NT</td>
</tr>
<tr>
<td>Uterus (non-gravid)</td>
<td>NT</td>
<td>-</td>
<td>NT</td>
</tr>
<tr>
<td>Placenta fluids</td>
<td>NT</td>
<td>NT</td>
<td>(-)</td>
</tr>
<tr>
<td>Fetus\textsuperscript{14}</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Embryos\textsuperscript{14}</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Musculoskeletal tissues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Heart/ pericardium</td>
<td>NT</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tendon</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
</tbody>
</table>
Table C: Tissues with no detected infectivity or PrP\textsuperscript{TSE} (continued)

<table>
<thead>
<tr>
<th>Tissues</th>
<th>Human TSEs</th>
<th>Cattle</th>
<th>Sheep &amp; goats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vCJD</td>
<td>Other TSEs</td>
<td>BSE</td>
</tr>
<tr>
<td>Infect-</td>
<td>PrP\textsuperscript{TSE}</td>
<td>Infect-</td>
<td>PrP\textsuperscript{TSE}</td>
</tr>
<tr>
<td>PrP\textsuperscript{TSE}</td>
<td>Infect-</td>
<td>PrP\textsuperscript{TSE}</td>
<td>Infect-</td>
</tr>
<tr>
<td>infectivity\textsuperscript{1}</td>
<td>infectivity\textsuperscript{1}</td>
<td>infectivity\textsuperscript{1}</td>
<td>infectivity\textsuperscript{1}</td>
</tr>
<tr>
<td>Other tissues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gingival tissue</td>
<td>NT</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dental pulp</td>
<td>NT</td>
<td>-</td>
<td>NT</td>
</tr>
<tr>
<td>Trachea</td>
<td>NT</td>
<td>-</td>
<td>NT</td>
</tr>
<tr>
<td>Skin</td>
<td>NT</td>
<td>-</td>
<td>NT</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>NT</td>
<td>-</td>
<td>(-)</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>NT</td>
<td>-</td>
<td>(-)</td>
</tr>
<tr>
<td>Mammary gland/udder</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Body fluids, secretions and excretions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk\textsuperscript{15}</td>
<td>NT</td>
<td>NT</td>
<td>(-)</td>
</tr>
<tr>
<td>Colostrum\textsuperscript{16}</td>
<td>NT</td>
<td>NT</td>
<td>(-)</td>
</tr>
<tr>
<td>Cord blood\textsuperscript{17}</td>
<td>NT</td>
<td>NT</td>
<td>(-)</td>
</tr>
<tr>
<td>Saliva</td>
<td>NT</td>
<td>-</td>
<td>NT</td>
</tr>
<tr>
<td>Sweat</td>
<td>NT</td>
<td>NT</td>
<td>-</td>
</tr>
<tr>
<td>Tears</td>
<td>NT</td>
<td>NT</td>
<td>-</td>
</tr>
<tr>
<td>Nasal mucus</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Bile</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Urine\textsuperscript{16,17}</td>
<td>NT</td>
<td>NT</td>
<td>-</td>
</tr>
<tr>
<td>Feces</td>
<td>NT</td>
<td>NT</td>
<td>-</td>
</tr>
</tbody>
</table>

14. Embryos from BSE-affected cattle have not transmitted disease to mice, but no infectivity measurements have been made with fetal calf tissues other than blood (negative mouse bioassay). Calves born of dams that received embryos from BSE-affected cattle have survived for observations periods of up to seven years, and examination of the brains of both the unaffected dams and their offspring revealed no spongiform encephalopathy or PrP\textsuperscript{TSE}.

15. Evidence that infectivity is not present in milk includes temporo-spatial epidemiologic observations failing to detect maternal transmission; clinical observations of over a hundred calves nursed by infected cows that have not developed BSE; and experimental observations that milk from infected cows has not transmitted disease when administered intracerebrally or orally to mice. Also, PrP\textsuperscript{TSE} has not been detected in milk from cattle incubating BSE following experimental oral challenge.

16. Early reports of transmission of CJD infectivity from human cord blood, colostrum, and urine have never been confirmed and are considered improbable. A recent bioassay in PrP over-expressing transgenic mice of colostrum from a cow with BSE gave a negative result; and PrP\textsuperscript{TSE} has not been detected in colostrum from cattle incubating BSE following experimental oral challenge.

17. IgG short chains mimicking the Western blot behavior of PrP\textsuperscript{TSE} have been identified in the urine of sporadic, variant, and familial CJD patients.
The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology 22–23 March 2006. Comments or objections to the decisions should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology at whocc@fhi.no before 1 September 2006. If no objections are received before this date, the new ATC codes and DDDs will be considered final and be included in the January 2007 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted through e-mail at: whocc@fhi.no.

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

<table>
<thead>
<tr>
<th>ATC level</th>
<th>INN/Common name</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents for age related macular degeneration</td>
<td></td>
<td>S01L¹</td>
</tr>
<tr>
<td>Angiotensin II antagonists and calcium channel blockers</td>
<td></td>
<td>C09DB</td>
</tr>
<tr>
<td>Antivirals for treatment of HIV infections, combinations</td>
<td></td>
<td>J05AR²</td>
</tr>
<tr>
<td>Insulins and analogues, for inhalation</td>
<td></td>
<td>A10AF</td>
</tr>
<tr>
<td>Ocular antineovascularization agents</td>
<td></td>
<td>S01LA</td>
</tr>
<tr>
<td>Papillomavirus vaccines</td>
<td></td>
<td>J07BM</td>
</tr>
</tbody>
</table>

¹ For the complete classification of S01L, see Summary of the main ATC alterations
² For the complete classification of J05AR, see Summary of the main ATC alterations

### New ATC 5th level codes:

- abatacept L04AA24
- aliskiren C09XA02
- ambrisentan C02KX02
- dasatinib L01XE06
- deferasirox V03AC03
- desvenlafaxine N06AX23
- emtricitabine, tenofovir disoproxil and efavirenz J05AR06
- fluocinolone acetonide S01BA15
- gadofosveset V08CA11
- garenoxacin J01MA19
- insulin (human) A10AF01
- medical air V03AN05
- nelarabine L01BB07
- nitrous oxide, combinations N01AX63
- panitumumab L01XC08
<table>
<thead>
<tr>
<th>ATC level</th>
<th>INN/Common name</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>papillomavirus</td>
<td>(human types 6, 11, 16, 18) J07BM01</td>
<td></td>
</tr>
<tr>
<td>ranibizumab</td>
<td></td>
<td>S01LA04</td>
</tr>
<tr>
<td>sitagliptin</td>
<td></td>
<td>A10BX05</td>
</tr>
<tr>
<td>telbivudine</td>
<td></td>
<td>J05AF11</td>
</tr>
<tr>
<td>valsartan and</td>
<td></td>
<td>C09DB01</td>
</tr>
<tr>
<td>amlodipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>varenicline</td>
<td></td>
<td>N07BA03</td>
</tr>
<tr>
<td>vildagliptin</td>
<td></td>
<td>A10BX06</td>
</tr>
<tr>
<td>zidovudine,</td>
<td>(and nevirapine)</td>
<td>J05AR05</td>
</tr>
<tr>
<td>lamivudine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>zoster, live</td>
<td>(attenuated)</td>
<td>J07BK02</td>
</tr>
<tr>
<td>attenuated</td>
<td></td>
<td></td>
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**ATC code changes** *(changes will not be implemented before January 2007)*

<table>
<thead>
<tr>
<th>INN/common name</th>
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<th>New ATC</th>
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<tbody>
<tr>
<td>anecortave</td>
<td>S01XA16</td>
<td>S01LA02</td>
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<tr>
<td>glyceryl trinitrate</td>
<td>D03AX07</td>
<td>C05AX06</td>
</tr>
<tr>
<td>isosorbide dinitrate</td>
<td>D03AX08</td>
<td>C05AX07</td>
</tr>
<tr>
<td>lamivudine and abacavir</td>
<td>J05AF30¹</td>
<td>J05AR02</td>
</tr>
<tr>
<td>pegaptanib</td>
<td>S01XA17</td>
<td>S01LA03</td>
</tr>
<tr>
<td>tenofovir disoproxil and emtricitabine</td>
<td>J05AF30¹</td>
<td>J05AR03</td>
</tr>
<tr>
<td>verteporfin</td>
<td>L01XD02</td>
<td>S01LA01</td>
</tr>
<tr>
<td>zidovudine and lamivudine</td>
<td>J05AF30¹</td>
<td>J05AR01</td>
</tr>
<tr>
<td>zidovudine, lamivudine and abacavir</td>
<td>J05AF30¹</td>
<td>J05AR04</td>
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</table>

¹ J05AF30: ATC level name: Combinations

**ATC name changes**

<table>
<thead>
<tr>
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<th>ATC code</th>
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<tbody>
<tr>
<td>Cytokines and immunomodulators</td>
<td>Cytokines and immunomodulators/stimulants</td>
<td>L03A</td>
</tr>
<tr>
<td>Immunostimulants</td>
<td>Immunomodulators/stimulants</td>
<td>L03</td>
</tr>
<tr>
<td>Immunosuppressive agents</td>
<td>Immunomodulators/suppressants</td>
<td>L04</td>
</tr>
<tr>
<td>Insulins and analogues, fast-acting</td>
<td>Insulins and analogues, fast-acting, for injection</td>
<td>A10AB</td>
</tr>
<tr>
<td>Insulins and analogues, intermediate-acting</td>
<td>Insulins and analogues intermediate-acting, for injection</td>
<td>A10AC</td>
</tr>
<tr>
<td>Insulins and analogues, intermediate-acting combined with fast-acting</td>
<td>Insulins and analogues, intermediate-acting combined with fast-acting, for injection</td>
<td>A10AD</td>
</tr>
<tr>
<td>Insulins and analogues, long-acting</td>
<td>Insulins and analogues, long-acting, for injection</td>
<td>A10AE</td>
</tr>
<tr>
<td>Other cytokines and immunomodulators/stimulants</td>
<td>Other cytokines and immunomodulators/stimulants</td>
<td>L03AX</td>
</tr>
<tr>
<td>Other immunosuppressive agents</td>
<td>Other immunomodulators/suppressants</td>
<td>L04AX</td>
</tr>
<tr>
<td>Selective immunosuppressive agents</td>
<td>Selective immunomodulators/suppressants</td>
<td>L04AA</td>
</tr>
</tbody>
</table>
### New DDDs:

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>DDD</th>
<th>Unit</th>
<th>Adm.R</th>
<th>ATC code</th>
</tr>
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<tbody>
<tr>
<td>entecavir</td>
<td>0.5</td>
<td>mg</td>
<td>O</td>
<td>J05AF10</td>
</tr>
<tr>
<td>erdosteine</td>
<td>0.6</td>
<td>g</td>
<td>O</td>
<td>R05CB15</td>
</tr>
<tr>
<td>estradiol</td>
<td>7.5</td>
<td>mcg</td>
<td>V</td>
<td>G03CA03</td>
</tr>
<tr>
<td>hydroxybutyric acid</td>
<td>7.5</td>
<td>g</td>
<td>O</td>
<td>N07XX04</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>30</td>
<td>mg²</td>
<td>P</td>
<td>C01EB16</td>
</tr>
<tr>
<td>ivabradine</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>C01EB17</td>
</tr>
<tr>
<td>natalizumab</td>
<td>10</td>
<td>mg</td>
<td>P</td>
<td>L04AA23</td>
</tr>
<tr>
<td>posaconazole</td>
<td>0.8</td>
<td>g</td>
<td>O</td>
<td>J02AC04</td>
</tr>
<tr>
<td>tipranavir</td>
<td>1</td>
<td>g</td>
<td>O</td>
<td>J05AE09</td>
</tr>
</tbody>
</table>

¹ vaginal ring, refers to amount delivered per 24 hours
² course dose

### Change of DDDs (Note that changes will not be implemented before January 2007)

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>Previous DDD</th>
<th>New DDD</th>
<th>ATC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>cefditoren</td>
<td>0.6 g O*</td>
<td>0.4 g O</td>
<td>cefditoren</td>
</tr>
</tbody>
</table>

* Temporary DDD from October 2005, has not been included in the ATC index.
ATC/DDD Classification

ATC/DDD classification (final)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in October 2005. They came into force on 1 February 2006 and will be included in the January 2007 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted through e-mail at: whocc@fhi.no.

<table>
<thead>
<tr>
<th>ATC level</th>
<th>INN/Common name</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>New ATC level codes (other than 5th level):</td>
<td>Protein kinase inhibitors</td>
<td>L01XE</td>
</tr>
<tr>
<td>New ATC 5th level codes:</td>
<td>aceclofenac</td>
<td>M02AA25</td>
</tr>
<tr>
<td></td>
<td>alendronic acid and colecalciferol</td>
<td>M05BB03</td>
</tr>
<tr>
<td></td>
<td>carteolol, combinations</td>
<td>S01ED55</td>
</tr>
<tr>
<td></td>
<td>ciprofloxacin</td>
<td>S02AA15</td>
</tr>
<tr>
<td></td>
<td>clindamycin, combinations</td>
<td>D10AF51</td>
</tr>
<tr>
<td></td>
<td>dapptomycin</td>
<td>J01XX09</td>
</tr>
<tr>
<td></td>
<td>darunavir</td>
<td>J05AE10</td>
</tr>
<tr>
<td></td>
<td>diclofenac</td>
<td>D11AX18</td>
</tr>
<tr>
<td></td>
<td>diphtheria- Haemophilus influenzae B-pertussis-tetanus-hepatitis B</td>
<td>J07CA11</td>
</tr>
<tr>
<td></td>
<td>diphtheria-pertussis-poliomyelitis-tetanus-hepatitis B</td>
<td>J07CA12</td>
</tr>
<tr>
<td></td>
<td>exenatide</td>
<td>A10BX04</td>
</tr>
<tr>
<td></td>
<td>febuxostat</td>
<td>M04AA03</td>
</tr>
<tr>
<td></td>
<td>glimepiride and rosiglitazone</td>
<td>A10BD04</td>
</tr>
<tr>
<td></td>
<td>glucarpidase</td>
<td>V03AF09</td>
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<tr>
<td></td>
<td>idursulfase</td>
<td>A16AB09</td>
</tr>
<tr>
<td></td>
<td>lenalidomide</td>
<td>L04AX04</td>
</tr>
<tr>
<td></td>
<td>moxifloxacin</td>
<td>S01AX22</td>
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<tr>
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<td>paliperidone</td>
<td>N05AX13</td>
</tr>
<tr>
<td></td>
<td>palonosetron</td>
<td>A04AA05</td>
</tr>
<tr>
<td></td>
<td>parathyroid hormone</td>
<td>H05AA03</td>
</tr>
<tr>
<td></td>
<td>pazufloxacin</td>
<td>J01MA18</td>
</tr>
<tr>
<td></td>
<td>pitavastatin</td>
<td>C10AA08</td>
</tr>
<tr>
<td></td>
<td>sorafenib</td>
<td>L01XE05</td>
</tr>
<tr>
<td></td>
<td>stiripentol</td>
<td>N03AX17</td>
</tr>
<tr>
<td></td>
<td>sunitinib</td>
<td>L01XE04</td>
</tr>
<tr>
<td></td>
<td>tigecycline</td>
<td>J01AA12</td>
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</table>
### ATC code changes (changes will not be implemented before January 2007)

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>Previous ATC</th>
<th>New ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>erlotinib</td>
<td>L01XX34</td>
<td>L01XE03</td>
</tr>
<tr>
<td>gefitinib</td>
<td>L01XX31</td>
<td>L01XE02</td>
</tr>
<tr>
<td>imatinib</td>
<td>L01XX28</td>
<td>L01XE01</td>
</tr>
<tr>
<td>ribavirin, combinations*</td>
<td>J05AB54</td>
<td>L03AB60</td>
</tr>
</tbody>
</table>

* See list of changed ATC level names

### ATC name changes

<table>
<thead>
<tr>
<th>Previous</th>
<th>New ATC</th>
<th>New ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates and calcium, sequential</td>
<td>Bisphosphonates, combinations</td>
<td>M05BB</td>
</tr>
<tr>
<td>Etidronic acid and calcium</td>
<td>Etidronic acid and calcium, sequential</td>
<td>M05BB01</td>
</tr>
<tr>
<td>Oral Blood glucose lowering drugs</td>
<td>Blood glucose lowering drugs, excluding insulins</td>
<td>A10B</td>
</tr>
<tr>
<td>Other oral blood glucose lowering drugs</td>
<td>Other blood glucose lowering drugs, excluding insulins</td>
<td>A10BX</td>
</tr>
<tr>
<td>Ribavirin, combinations</td>
<td>Peginterferon alfa-2b, combinations</td>
<td>L03AB60**</td>
</tr>
<tr>
<td>Risedronic acid and calcium</td>
<td>Risedronic acid and calcium, sequential</td>
<td>M05BB02</td>
</tr>
<tr>
<td>Varicella vaccines</td>
<td>Varicella zoster vaccines</td>
<td>J07BK</td>
</tr>
<tr>
<td>Varicella, live attenuated</td>
<td>Varicella zoster, live attenuated</td>
<td>J07BK01</td>
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</tbody>
</table>

** See list of changed ATC codes

### New DDDs:

<table>
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<tr>
<th>INN/common name</th>
<th>DDD</th>
<th>Unit</th>
<th>Adm.R</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>benfluorex</td>
<td>0.45</td>
<td>g</td>
<td>O</td>
<td>C10AX04</td>
</tr>
<tr>
<td>cefditoren</td>
<td>0.6</td>
<td>g</td>
<td>O</td>
<td>J01DD16</td>
</tr>
<tr>
<td>cyanocobalamin</td>
<td>70</td>
<td>mcg</td>
<td>N</td>
<td>B03BA01</td>
</tr>
<tr>
<td>daptomycin</td>
<td>0.28</td>
<td>g</td>
<td>P</td>
<td>J01XX09</td>
</tr>
<tr>
<td>desmopressin</td>
<td>0.36</td>
<td>g base</td>
<td>SL</td>
<td>H01BA02</td>
</tr>
<tr>
<td>ibandronic acid</td>
<td>5</td>
<td>mg</td>
<td>O</td>
<td>M05BA06</td>
</tr>
<tr>
<td>imidapril</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>C09AA16</td>
</tr>
<tr>
<td>interferon alfa natural</td>
<td>2</td>
<td>MU</td>
<td>P</td>
<td>L03AB01</td>
</tr>
<tr>
<td>lanreotide</td>
<td>3</td>
<td>mg</td>
<td>P</td>
<td>H01CB03</td>
</tr>
<tr>
<td>mecobalamin</td>
<td>1.5</td>
<td>mg</td>
<td>O</td>
<td>B03BA05</td>
</tr>
<tr>
<td>mecobalamin</td>
<td>0.2</td>
<td>mg</td>
<td>P</td>
<td>B03BA05</td>
</tr>
<tr>
<td>mesna</td>
<td>1.2</td>
<td>g</td>
<td>Inh</td>
<td>R05CB05</td>
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<tr>
<td>naftidofuryl</td>
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<td>O</td>
<td>C04AX21</td>
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<tr>
<td>palifermin</td>
<td>4.2</td>
<td>mg</td>
<td>P</td>
<td>V03AF08</td>
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<td>palonosetron</td>
<td>0.25</td>
<td>mg</td>
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<td>A04AA05</td>
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<td>pazufloxacin</td>
<td>1</td>
<td>g</td>
<td>P</td>
<td>J01MA18</td>
</tr>
<tr>
<td>piribedil</td>
<td>0.2</td>
<td>g</td>
<td>O</td>
<td>N04BC08</td>
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<td>pitavastatin</td>
<td>2</td>
<td>mg</td>
<td>O</td>
<td>C10AA08</td>
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<td>pyritinol</td>
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<td>g</td>
<td>O</td>
<td>N06BX02</td>
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<tr>
<td>rasagiline</td>
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<td>mg</td>
<td>O</td>
<td>N04BD02</td>
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<tr>
<td>tegaserod</td>
<td>12</td>
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<td>O</td>
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**New DDDs (continued):**

<table>
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<tr>
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<th>DDD</th>
<th>Unit</th>
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<th>ATC code</th>
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<td>testosterone</td>
<td>60 mg</td>
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<tr>
<td>tianeptine</td>
<td>37.5 mg</td>
<td></td>
<td>O</td>
<td>N06AX14</td>
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<tr>
<td>trimebutine</td>
<td>0.6 g</td>
<td></td>
<td>O</td>
<td>A03AA05</td>
</tr>
<tr>
<td>ziconotide</td>
<td>12 mcg</td>
<td></td>
<td>P</td>
<td>N02BG08</td>
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</table>

**Change of DDDs** *(changes to be implemented in January 2007)*

<table>
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<th>New DDD</th>
<th>ATC Code</th>
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<tr>
<td>cinacalcet</td>
<td>90 mg O*</td>
<td>60 mg O</td>
<td>H05BX01</td>
</tr>
<tr>
<td>ibandronic acid</td>
<td>2.5 mg O*</td>
<td>5 mg O</td>
<td>M05BA06</td>
</tr>
<tr>
<td>ibandronic acid</td>
<td>4 mg P</td>
<td>6 mg P</td>
<td>M05BA06</td>
</tr>
</tbody>
</table>

* Temporary DDD, has not been included in the ATC index

* Temporary DDD from October 2005, has not been included in the ATC index.
Recent Publications, Information and Events

Interagency Emergency Health Kit 2006

Over the years, the concept of the emergency health kit has been adopted by many organizations and national authorities as a reliable, standardized and quickly available source of essential medicines and medical devices (renewables and equipment) urgently needed in a disaster situation.

The Interagency Emergency Health Kit 2006 (IEHK 2006) is now available on the WHO Medicines website. This is the third edition of the WHO Emergency Health Kit initially launched in 1990. This is an initiative of WHO in collaboration with a large number of organizations and agencies of the United Nations system and international and non-governmental organizations.

The aim of the emergency health kit is to encourage standardization of medicines and medical supplies (renewables and equipment) needed in emergencies and disasters. This will permit an effective response with medicines and medical devices by means of standard, pre-packed kits that could be kept in readiness to meet priority health needs in disaster situations. Its content is based on the health needs of 10,000 persons for a period of three months.

WHO encourages all countries, national and international organizations, agencies and donors to use The Interagency Emergency Health Kit 2006 when being called upon to respond urgently to emergencies or disasters.


Therapeutic guidelines for rheumatology

The Therapeutic Guidelines range has become well known internationally. The guidelines are independent, peer reviewed and regularly updated. Therapeutic Guidelines: Rheumatology, have just been released covering management of a wide range of musculoskeletal conditions.

This title addresses several issues of current global interest. The section ‘Getting to know Your Drugs’ explains the role of appropriate drugs for the management of painful musculoskeletal conditions in an era where it has been hard to find safe new drugs for pain management.

This edition also features non-drug interventions and very clear diagrams and instructions for exercises which have been found to be most beneficial in the management of pain. Therapeutic Guidelines: Rheumatology also includes sections on children and adolescents and management of conditions during pregnancy and breastfeeding.


Specifications for pharmaceutical preparations

The WHO Expert Committee on Specifications for Pharmaceutical Preparations meets every two years. The following is a list of reports and guidelines included in the Fortieth report of the Expert Committee recently published by WHO.


Annex 2 Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms.

Annex 3 Supplementary guidelines on good manufacturing practices for the manufacture of herbal medicines.

Annex 4 Supplementary guidelines on good manufacturing practices: validation.
Annex 5  Good distribution practices for pharmaceutical products.

Annex 6  A model quality assurance system for procurement agencies.

Annex 7  Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability.

Annex 8  Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms.

Annex 9  Additional guidance for organizations performing in vivo bioequivalence studies.


New guidance for pharmacists on counterfeit medicines

The Medicines and Healthcare Products Regulatory Agency (MHRA) and the Royal Pharmaceutical Society of Great Britain (RPSGB) have published new guidance for pharmacists which explains the causes and consequences of counterfeiting and provides pharmacists with practical advice on detecting and reporting suspected counterfeit medicines.


Marketed unapproved drugs — policy guide

For historical reasons, some drugs are available in the United States that lack required FDA approval for marketing. The new drug approval and OTC drug monograph processes play an essential role in ensuring that all drugs are both safe and effective for their intended uses. Manufacturers of drugs that lack required approval, including those that are not marketed in accordance with an OTC drug monograph, have not provided evidence demonstrating safety and efficacy.

FDA is taking steps to either encourage the manufacturers of these products to obtain the required evidence and comply with approval provisions or remove the products from the market. In order to achieve these goals without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market, the FDA has issued Guidance for FDA Staff and Industry. Marketed Unapproved Drugs — Compliance Policy Guide which describes how FDA intend to exercise enforcement discretion with regard to drugs marketed in the United States that do not have required FDA approval for marketing. It applies to any drug required to have FDA approval for marketing, including new drugs covered by the Over-the-Counter (OTC) Drug Review, except for licensed biologics and veterinary drugs.

A brief, informal summary description of the various categories of these drugs and their regulatory status is provided in Appendix A as general background for the document. The manufacturers of these drugs have not received FDA approval to legally market


WHO guidelines on avian influenza

WHO guidelines on avian influenza have been developed based on a rapid review of available evidence. These are available on the WHO Website.

Feedback on their usefulness would be very much appreciated, as they have been developed based on a rapid review of available evidence. The objective is to link recommendations explicitly to the quality of evidence currently available.

WHO analgesic ladder

An appraisal of the WHO Analgesic Ladder is the focus of the current issue of Cancer Pain Release, the publication of the WHO Pain and Palliative Care Communications Programme. The issue features an interview with Dr. Kathleen Foley, former chair of the WHO Expert Committee on Cancer Pain Relief and Active Supportive Care, the group that drafted Cancer pain relief (2). The WHO guidelines also include foundation measures for implementing cancer pain relief programmes and improving opioid availability.

The issue (available in English, French, Spanish and Russian) highlights research on the WHO Analgesic Ladder and provides online links to WHO source documents about the method to relieve cancer pain.

References

Resources for paediatric formulations

The British Neonatal and Paediatric Pharmacists Group has many useful links on their Website. Under the “Pharmaceutical links” category there is a “Formulation and stability database”. The information in the database was gathered from hospitals throughout the UK and published documents.

Reference: http://www.nppg.org.uk/
Consultation Document

International Pharmacopoeia: Revision of monographs for antimalarials and draft proposals for antiretrovirals

All monographs published in The International Pharmacopoeia on artemisin derivatives, (i.e. artemether, artemisinin, artemotil, and artemimol as active ingredients and dosage forms) have the same limits for the related substances tests (HPLC and TLC) with the exception of artesunate. Artesunate (active ingredient and tablets) has higher limits than the others due to the fact that this substance was considered to be less stable. However, comments received from different parties and experimental verification by the WHO Collaborating Centre for Drug Quality Assurance, People’s Republic of China, suggest that the limits on artesunate should be reconsidered and brought in line with the other International Pharmacopoeia monographs on artemisinin derivatives. In addition, in all monographs on artemisinin derivatives except artesunate, a test for loss of drying is described. For artesunate, a test for water content is described. The proposals below would bring the monographs on artesunate in line with the other artemisinin derivative monographs.

Please address any comments you may have to: Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: kopps@who.int and rabouhansm@who.int.

Artesunate

Related substances
It is proposed to amend the limits as follows:

HPLC

- Any impurity: not more than 0.5% (instead of 1.0%)
- Not more than one impurity above 0.25% (instead of 0.5%)
- Total of impurities: not more than 1.0% (instead of 2.0%)
- Disregard limit: 0.05% (instead of 0.1%)

TLC

- Any impurity spot is not more intense than 0.5% (instead of 1.0%)
- Not more than one impurity spot is more intense than 0.25% (instead of 0.5%)

HPLC assay limits
If it is agreed to revise the related substances tests as proposed above, consideration should be given to revising the HPLC assay limits to 97.0%–102.0% (instead of 96.0%–102.0%).
**Water**
It is proposed to replace the test for water by a test on loss of drying.

Drying at 60 °C under reduced pressure (not more than 2.67 kPa) has been suggested. The test could either specify drying to constant mass (as artemisinin) or specify a time, if a suitable time is available.

A suitable limit will need to be agreed (e.g. 0.5 % as for artemether or 1.0 % as for artemimol may be suitable).

*Note: The basis in which the assay limits are calculated would need to be changed from the anhydrous to the dried substance.*

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**Artesunate tablets**

**Related substances (HPLC and TLC)**
If it is agreed to revise the limits in the related substances tests for the active ingredient, it is proposed that the limits for the tablets would need to be revised to maintain consistency.

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**International Pharmacopoeia:**
**Draft proposals for antiretroviral dosage forms**

**Lamivudine oral solution**

*Draft proposal for The International Pharmacopoeia (May 2006). Please address any comments you may have to: Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: kopps@who.int and rabouhansm@ who.int.*

**Category.** Antiretroviral (nucleoside reverse transcriptase inhibitor).

**Storage.** Lamivudine oral solution should be kept in a well-closed container, protected from light and at a temperature below 25 °C.

**Additional Information:** Strength in the current WHO Model List of Essential Medicines: 50 mg per 5 ml (10 mg per ml).

**Requirements**
Complies with the monograph for “Liquids for Oral Use”.

*Note from Secretariat: A general monograph is in preparation.*

**Definition.** Lamivudine oral solution is a solution of Lamivudine in a suitable flavoured vehicle. It contains not less than 90.0 % and not more than 110.0 % of the amount of lamivudine, C$_8$H$_{11}$N$_3$O$_3$S stated on the label.

*Refers to The International Pharmacopoeia*
Identity tests

A. Carry out test A.1. or where UV detection is not available, test A.2.

A.1. Carry out the test as described under 1.14.1 Thin-layer chromatography*, using silica gel R6 as the coating substance and a mixture of 67 volumes of dichloromethane R, 20 volumes of acetonitrile R, 10 volumes of methanol R and 3 volumes of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 µl of each of the following 2 solutions. For solution (A), dilute a volume of the oral solution containing 50 mg of Lamivudine to 50 ml with methanol R, filter, and use the filtrate. For solution (B), use 1.0 mg of lamivudine RS per ml of methanol. After removing the plate from the chromatographic chamber, allow it to dry in a current of cool air, and examine the chromatogram in ultraviolet light (254 nm).

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

A.2. Carry out the test as described under 1.14.1 Thin-layer chromatography*, using silica gel R5 as the coating substance and a mixture of 67 volumes of dichloromethane R, 20 volumes of acetonitrile R, 10 volumes of methanol R and 3 volumes of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 µl of each of the following 2 solutions. For solution (A), dilute a volume of the oral solution containing 50 mg of Lamivudine to 50 ml with methanol R, filter, and use the filtrate. For solution (B), use 1.0 mg of lamivudine RS per ml of methanol. After removing the plate from the chromatographic chamber, allow it to dry in a current of cool air. Spray with vanillin/sulfuric acid TS1. Heat the plate for a few minutes at 120 ˚C. Examine the chromatogram in daylight.

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

B. See the test described below under Assay A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that obtained with solution (2).

C. The absorption spectrum of the final solution prepared for assay method B, when observed between 210 nm and 300 nm, exhibits one maximum at about 280 nm; the specific absorbance (A 1% 1cm) is between 577 to 637.

Related substances

Carry out the test as described under 1.14.4 high-performance liquid chromatography*, using a stainless steel column (25 cm x 4.6 mm) packed with base deactivated particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm) (Hypersil® BDS C18 is suitable). As the mobile phase, use a mixture of 5 volumes of methanol R and 95 volumes of buffer 3.8 (a 1.9 g/l solution of ammonium acetate R previously adjusted to pH 3.8 with glacial acetic acid R).

Prepare the following solutions. For solution (1), mix a quantity of the oral solution containing 50 mg of Lamivudine with sufficient mobile phase to produce 100 ml and filter. For solution (2), dilute 1.0 ml of solution (1) to 100 ml with mobile phase.

For the system suitability test: prepare solution (3) in the mobile phase containing about 10 µg of impurity B RS and 200 µg of lamivudine RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of about 277 nm. Maintain the temperature of the column at 35 ºC.

* Refers to The International Pharmacopoeia
Inject separately 20 µl each of solutions (1), (2) and (3). Record the chromatograms for about 3 times the retention time of lamivudine in solution (2). The test is not valid unless in the chromatogram obtained with solution (3) the resolution factor between the peaks due to lamivudine and impurity B is greater than 1.5.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). In the chromatogram obtained with solution (1), the area of any peak, other than the principal peak, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5 %), the area of not more than one such peak is greater than 0.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%), and the area of not more than two such peaks is greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3 %). The sum of the areas of all peaks, other than the principal peak, is not greater than 3 times the area of the principal peak obtained with solution (2) (3.0%). Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (2) (0.05 %).

**Assay**
Either test A or B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography*, using the conditions given above under Related Substances*. Prepare the following solutions in the mobile phase. For solution (1), mix a quantity of the oral solution containing 50 mg of Lamivudine with sufficient mobile phase to produce 100 ml and dilute 10 ml to 25 ml with mobile phase. Filter a portion of this solution through a 0.45 µm filter, discarding the first few ml of the filtrate. For solution (2), use 0.2 mg of lamivudine RS per ml.

Inject 20 µl of solution (2) in six replicate injections into the chromatographic system. The assay is not valid unless the relative standard deviation for the peak area of lamivudine is less than 2.0 %

Inject separately 20 µl each of solutions (1) and (2).

Measure the areas of the peaks responses obtained in the chromatograms of solutions (1) and (2). Calculate the percentage content of lamivudine (C₈H₁₁N₃O₃S).

B. Dilute a volume of the oral solution containing 50 mg of Lamivudine to 50 ml with water. Add 1 ml of sulfuric acid (0.1 mol/l) VS and extract with two 30 ml quantities of diethyl ether R. Wash the combined ether extracts with 20 ml of water, combine the aqueous solutions and remove the ether using a current of nitrogen. Add sufficient water to produce 200 ml and dilute 5 ml to 50 ml with sulfuric acid (0.1 mol/l) VS. Measure the absorbance of the resulting solution in a 1 cm layer at the maximum at 280 nm against a solvent cell containing the blank. For the blank, use a solution prepared by diluting 1 ml of sulfuric acid (0.1 mol/l) VS to 200 ml with water and further dilute 5 ml of this solution to 50 ml with sulfuric acid (0.1 mol/l) VS. Calculate the percentage content of lamivudine, C₈H₁₁N₃O₃S using the absorptivity value of 60.7 (A₁%1cm = 607).

**Lamivudine compressi**
**Lamivudine tablets**

_Draft proposal for The International Pharmacopoeia (May 2006). Please address any comments you may have to: Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: kopps@who.int and rabouhansm@who.int._

**Category.** Antiretroviral (nucleoside reverse transcriptase inhibitor).

*Refers to The International Pharmacopoeia*
Storage. Lamivudine tablets should be kept in a well-closed container, protected from light.

Additional information. Strength in the current WHO Model List of Essential Medicines: 150 mg, 300 mg. The tablets may be uncoated or coated.

Requirements

Comply with the monograph for “Tablets”.

Lamivudine tablets contain Lamivudine. They contain not less than 90.0 % and not more than 110.0 % of the amount of lamivudine, \( \text{C}_8\text{H}_{11}\text{N}_3\text{O}_3\text{S} \) stated on the label.

Identity tests

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

A. Carry out test A.1. or, where UV detection is not available, test A.2.

A.1. Carry out the test as described under 1.14.1 Thin-layer chromatography*, using silica gel R6 as the coating substance and a mixture of 67 volumes of dichloromethane R, 20 volumes of acetonitrile R, 10 volumes of methanol R and 3 volumes of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 \( \mu \)l of each of the following 2 solutions. For solution (A), shake a quantity of the powdered tablets containing about 50 mg of Lamivudine with 50 ml of methanol R, filter, and use the filtrate. For solution (B), use 1.0 mg of lamivudine RS per ml of methanol. After removing the plate from the chromatographic chamber, allow it to dry in a current of cool air, and examine the chromatogram in ultraviolet light (254 nm).

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

A.2. Carry out the test as described under 1.14.1 Thin-layer chromatography*, using silica gel R5 as the coating substance and a mixture of 67 volumes of dichloromethane R, 20 volumes of acetonitrile R, 10 volumes of methanol R and 3 volumes of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 \( \mu \)l of each of the following 2 solutions. For solution (A), shake a quantity of the powdered tablets containing about 50 mg of lamivudine with 50 ml of methanol R, filter, and use the filtrate. For solution (B), use 1.0 mg of lamivudine RS per ml of methanol. After removing the plate from the chromatographic chamber, allow it to dry in a current of cool air. Spray with vanillin/sulfuric acid TS1. Heat the plate for a few minutes at 120 °C. Examine the chromatogram in daylight.

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

B. See the test described below under Assay A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that obtained with solution (2).

C. The absorption spectrum of the final solution prepared for assay method B, when observed between 210 nm and 300 nm, exhibits one maximum at about 280 nm; the specific absorbance (A1%1cm) is between 577 to 637.

D. To a quantity of the powdered tablets containing 50 mg of Lamivudine add 20 ml of methanol R, shake to dissolve, and filter. Evaporate the filtrate in a stream of nitrogen and, using the test residue thus obtained, carry out the examination as described under 1.7 spectrophotometry in

* Refers to The International Pharmacopoeia
the infrared region*. The infrared absorption spectrum is concordant with the spectrum obtained from lamivudine RS or with the reference spectrum of lamivudine.

If the spectra thus obtained are not concordant, repeat the test using the test residue and the residue obtained by dissolving lamivudine RS in methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from lamivudine RS.

Related substances

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with base deactivated particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm). (Hypersil® BDS C18 is suitable.) As the mobile phase, use a mixture of 5 volumes of methanol R and 95 volumes of buffer pH 3.8 (a 1.9 g/l solution of ammonium acetate R, previously adjusted to pH 3.8 with glacial acetic acid R).

Prepare the following solutions. For solution (1), weigh and powder 20 tablets. To a quantity of the powder containing about 50 mg of Lamivudine, add 60 ml of mobile phase and dissolve using an ultrasonic bath if necessary. Dilute to 100 ml with mobile phase. Filter and use the filtrate. For solution (2), dilute 1.0 ml of solution (1) to 100 ml with the mobile phase and then dilute 1.0 ml of this solution to 10 ml.

For the system suitability test: prepare solution (3) in the mobile phase containing about 10 µg of impurity B RS and 200 µg of lamivudine RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of about 277 nm. Maintain the temperature of the column at 35 °C. Inject separately 20 µl each of solutions (1), (2) and (3). Record the chromatograms for about 3 times the retention time of lamivudine in solution (2). The test is not valid unless in the chromatogram obtained with solution (3) the resolution factor between the peaks due to lamivudine and impurity B is greater than 1.5.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). In the chromatogram obtained with solution (1), the area of any peak, other than the principal peak, is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3 %); the area of not more than one such peak is greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2 %) and the area of Not more than two such peaks is greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1 %). The sum of the areas of all peaks, other than the principal peak, is not greater than 6 times the area of the principal peak obtained with solution (2) (0.6 %). Disregard any peak with an area less than 0.5 times the area of the principal peak obtained with solution (2) (0.05 %).

Either test A or B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography*, using the conditions given above under Related substances*. Prepare the following solutions in the mobile phase. For solution (1), weigh and powder 20 tablets. To a quantity of the powder containing about 50 mg of Lamivudine, add 60 ml of mobile phase and dissolve using an ultrasonic bath if necessary. Dilute to 100 ml with mobile phase. Filter a portion of this solution through a 0.45 µm filter, discarding the first few ml of the filtrate. Dilute 10 ml of the filtrate to 25 ml with mobile phase. For solution (2), use 0.2 mg of lamivudine RS per ml.

Inject separately 20 µl of solution (2) in six replicate injections in the chromatographic system. The assay is not valid unless the relative standard deviation for the peak area of lamivudine is less than 2.0 %.

* Refers to The International Pharmacopoeia
 Inject alternately 20 µl each of solutions (1) and (2).

Measure the areas of the peaks responses of lamivudine obtained in the chromatograms of solutions (1) and (2). Calculate the percentage content of lamivudine, C₈H₁₁N₃O₃S.

B. Weigh and powder 20 tablets. Transfer a quantity of the powder containing about 50 mg of Lamivudine, accurately weighed, to a 500 ml volumetric flask. Add about 400 ml of water and dissolve using an ultrasonic bath if necessary. Make up to volume with water. Filter a portion of this solution through a 0.45 µm filter, discarding the first few ml of the filtrate. Dilute 5 ml of this solution to 50 ml with sulfuric acid (0.1 mol/l) VS. Measure the absorbance of this solution in a 1 cm layer at the maximum about 280 nm against a solvent cell containing the blank. For the blank, use a solution prepared by diluting 5 ml of water with 50 ml of sulfuric acid (0.1 mol/l) VS.

Calculate the percentage content of lamivudine, C₈H₁₁N₃O₃S using the absorptivity value of 60.7 (A¹%1cm = 607).

**Zidovudine and lamivudine tablets**

*Draft proposal for The International Pharmacopoeia (May 2006). Please address any comments you may have to: Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: kopps@who.int and rabouhansm@who.int.*

**Category.** Antiretroviral (nucleoside reverse transcriptase inhibitor).

**Storage.** Zidovudine and Lamivudine tablets should be kept in a tightly closed container, protected from light.

**Additional information.** Strengths in the current WHO Model List of Essential Drugs: 300 mg Zidovudine and 150 mg Lamivudine. The tablets may be uncoated or coated.

**REQUIREMENTS**

Comply with the monograph for "Tablets".

**Definition.** Zidovudine and lamivudine tablets contain zidovudine and lamivudine. They contain not less than 90.0 % and not more than 110.0 % of the amounts of zidovudine (C₁₀H₁₃N₅O₄) and lamivudine (C₈H₁₁N₃O₃S) stated on the label.

**Identity tests**

A. Carry out test A.1. or, where UV detection is not available, test A.2.

A.1. Carry out the test as described under 1.14.1 Thin-layer chromatography*, using silica gel R6 as the coating substance and a mixture of 90 volumes of dichloromethane R, 10 volumes of methanol R and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 µl of each of the following 2 solutions. For solution (A), shake a quantity of the powdered tablets equivalent to about 50 mg of Lamivudine (about 100 mg of Zidovudine) with 50 ml of methanol R, filter, and use the filtrate. For solution (B), use 2.0 mg of zidovudine RS and 1.0 mg of lamivudine RS per ml of methanol. After removing the plate from the chromatographic chamber, allow it to dry in a current of cool air, and examine the chromatogram in ultraviolet light (254 nm).

*Refers to The International Pharmacopoeia
The two principal spots obtained with solution A correspond in position, appearance, and intensity with those obtained with solution B.

A.2. Carry out the test as described under 1.14.1 Thin-layer chromatography*, using silica gel R5 as the coating substance and a mixture of 90 volumes of dichloromethane R, 10 volumes of methanol R and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 µl of each of the following 2 solutions. For solution (A), shake a quantity of the powdered tablets equivalent to about 50 mg of Lamivudine (about 100 mg of Zidovudine) with 50 ml of methanol R, filter, and use the filtrate. For solution (B), use 2.0 mg of zidovudine RS and 1.0 mg of lamivudine RS per ml of methanol. After removing the plate from the chromatographic chamber, allow it to dry in a current of cool air. Dip the plate in dilute basic potassium permanganate (1 g/l) TS. Examine the chromatogram in daylight.

The two principal spots obtained with solution A correspond in position, appearance, and intensity with those obtained with solution B.

B. See the test described below under assay. The retention times of the principal peaks in the chromatogram obtained from solution (1) of assay are similar to those obtained from solution (2) of assay.

[Note from Secretariat: The possibility of additional tests for Identity is under investigation.]

Related Substances

Carry out the test as described under 1.14.4 High-performance liquid chromatography*, using a stainless steel column (25 cm x 4.6 mm) packed with base deactivated particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm). Use a mixture of 5 volumes of methanol R and 95 volumes of buffer pH 3.8 (a 1.9 g/l solution of ammonium acetate R, previously adjusted to pH 3.8 with glacial acetic acid R) as the mobile phase A. Use 100% methanol as mobile phase B.

For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powder containing about 100 mg of Zidovudine (about 50 mg of Lamivudine) into a 100 ml volumetric flask. Add about 50 ml of mobile phase A and dissolve by sonicating for 15 minutes. Dilute to volume with the same solvent and mix. Filter through a 0.45 µm filter, discarding the first few ml of the filtered solution. For solution (2), dissolve 2 mg of thymine R in 10 ml of methanol R. Then dilute 2 ml to 20 ml with the mobile phase A. For solution (3), dissolve 1 mg of zidovudine impurity B RS (3'-chloro-3'-deoxythymidine) in 10 ml of methanol R. Then dilute 2 ml to 20 ml with the mobile phase A. For solution (4), dilute 1 ml of solution (1) to 100 ml with mobile phase A.

For the system suitability test: prepare solution (5) in mobile phase A containing about 10 µg per ml of lamivudine impurity B RS, 200 µg per ml of lamivudine RS, 400 µg per ml of zidovudine RS and 10 µg per ml of zidovudine impurity B RS.

Use the following gradient elution:

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>% A</th>
<th>% B</th>
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<tbody>
<tr>
<td>0 – 30</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>30 – 40 (linear gradient)</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>40 – 45 (hold)</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>45 – 55 (linear gradient)</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

* Refers to The International Pharmacopoeia
Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 270 nm.

Inject separately 20 µl each of solutions (1), (2), (3), (4) and (5).

The test is not valid unless in the chromatogram obtained with solution (5), the resolution between lamivudine (retention time about 9 minutes) and lamivudine impurity B (relative retention time is about 0.92 with reference to lamivudine) is greater than 1.5 and the resolution between zidovudine (retention time about 42 minutes) and zidovudine impurity B (relative retention time is about 1.03 with reference to zidovudine) is greater than 2.0.

In the chromatogram obtained with solution (1), the area of any peak corresponding to the impurity with a relative retention time of about 0.40 with respect to lamivudine is not greater than 0.3 times the area of the lamivudine peak in the chromatogram obtained with solution (4) (0.3 %). The area of any peak corresponding to the impurity with a relative retention time of about 0.92 with respect to lamivudine is not greater than 0.2 times the area of the lamivudine peak in the chromatogram obtained with solution (4) (0.2 %). The area of any peak corresponding to thymine is not greater than the area of the peak in the chromatogram obtained with solution (2) (2 % with respect to zidovudine). The area of any peak corresponding to 3'-chloro-3'-deoxythymidine is not greater than the area of the peak in the chromatogram obtained with solution (3) (1 % with respect to zidovudine).

**Assay**

Carry out the test as described under 1.14.4 High-performance liquid chromatography*, using the conditions given above under Related Substances*. For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powder containing about 300 mg of Zidovudine (about 150 mg of Lamivudine) into a 100 ml volumetric flask. Add about 50 ml of mobile phase A and dissolve by sonicating for 15 minutes. Dilute to volume with the same solvent and mix. Filter through a 0.45 µm filter, discarding the first few ml of the filtered solution. Dilute 5 ml of the filtrate to 50 ml with the same solvent. For solution (2), prepare a 0.3 mg/ml solution of zidovudine RS and 0.15 mg/ml of lamivudine RS in mobile phase A.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 270 nm.

Inject separately 20 µl of solution (2) in six replicate injections in the chromatographic system. The assay is not valid unless the relative standard deviation for the peak area of both zidovudine and lamivudine is less than 2.0 %.

Inject alternately 20 µl each of solutions (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the percentage content of zidovudine \((\text{C}_{10}\text{H}_{13}\text{N}_5\text{O}_4)\) and lamivudine \((\text{C}_{8}\text{H}_{11}\text{N}_3\text{O}_3\text{S})\).

*Refers to The International Pharmacopoeia
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 (1–91) and Recommended (1–52) International Nonproprietary Names can be found in Cumulative List No. 11, 2004 (available in CD-ROM only). The statements indicating action and use are based largely on information supplied by the manufacturer. This information is merely meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature, these descriptors will neither be revised nor included in the Cumulative Lists of INNs.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Il est notifié que, conformément aux dispositions de l'article 3 de la Procédure à suivre en vue de choisir les 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 (1–91) et recommandées (1–52) dans la Liste récapitulative No. 11, 2004 (disponible sur CD-ROM seulement). Les mentions indiquant les propriétés et les indications des substances sont fondées sur les renseignements communiqués par le fabricant. Elles ne visent qu'à donner une idée de l'utilisation potentielle des nouvelles substances au moment où elles sont l'objet de propositions de DCI. L'OMS n'est pas en mesure de confirmer ces déclarations ni de faire de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations ne figureront pas dans les listes récapitulatives de DCI.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

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

Las listas de Denominaciones Comunes Internacionales Propuestas (1–91) y Recomendadas (1–52) se encuentran reunidas en Cumulative List No. 11, 2004 (disponible sólo en CD-ROM). Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deben incluirse en las listas recapitulativas de DCI.
Proposed International Nonproprietary Names: List 95
Publication date: 21 August 2006
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 95 Proposed INN not later than 21 December 2006.

Dénominations communes internationales proposées: Liste 95
Date de publication: 21 août 2006.
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 95 de DCI Proposées le 21 décembre 2006 au plus tard.

Denominaciones Comunes Internacionales Propuestas: Lista 95
Fecha de la publicación: el 21 de agosto de 2006
Cualquier persona puede dirigir observaciones u objeciones respecto de las denominaciones propuestas, al Programa de Denominaciones Comunes Internacionales de la Organización Mundial de la Salud, en un plazo de cuatro meses, contados desde la fecha de su publicación en WHO Drug Information, es decir, para la Lista 95 de DCI Propuestas el 21 de diciembre de 2006 a más tardar.

| Proposed INN (Latin, English, French, Spanish) | Chemical name or description: Action and use: Molecular formula | Chemical Abstracts Service (CAS) registry number: Graphic formula
| DCI Proposée | Nom chimique ou description: Propriétés et indications: Formule brute | Numéro dans le registre du CAS: Formule développée
| DCI Propuesta | Nombre químico o descripción: Acción y uso: Fórmula molecular | Número de registro del CAS: Fórmula desarrollada

abagovomabum*
abagovomab immunoglobulin G1, anti-idiotype anti-[anti-\{Homo sapiens cancer antigen 125, CA 125, MUC-16\} Mus musculus monoclonal antibody OC125] Mus musculus monoclonal antibody ACA125, clone 3D5 gamma1 heavy chain disulfide with clone 3D5 kappa light chain; (223-223\':226-226\':228-228\') trisdisulfide dimer immunological agent, antineoplastic

abagovomab
abagovomab immunoglobuline G1, anti-idiotype anti-[anti-\{Homo sapiens cancer antigen 125, CA 125, MUC-16\} anticorps monoclonal murin OC125] anticorps monoclonal murin ACA125, chaîne lourde gamma1 du clone 3D5 unie par un pont disulfure à la chaîne légère kappa du clone 3D5; dimère (223-223\':226-226\':228-228\')-trisdisulfure agent immunologique, antinéoplasique

abagovomab
abagovomab immunoglobulina G1, anti-idiotipo anti-[anti-\{Homo sapiens cancer antígeno 125, CA 125, MUC-16\} anticuerpo monoclonal murino OC125] anticuerpo monoclonal murino ACA125, cadena pesada gamma1 del clon 3DS unida por un puente disulfuro a la cadena ligera kappa del clon 3DS; dimero (223-223\':226-226\':228-228\')-trisdisulfuro agente inmunológico, antineoplásico
acidum iodofilticum (\(^{123}\)I)

iodofiltic acid (\(^{123}\)I)

\((3R)-15-[4-\text{Iodophenyl}]3\text{-methylpentadecanoic acid}
\)

radiopharmaceutical

acide iodofiltique (\(^{123}\)I)

acide (3RS)-15-[4-[\text{Iodophényl}]-3-méthylpentadécanoïque

radiopharmaceutique

ácido iodofíltico (\(^{123}\)I)

ácido (3RS)-15-[4-[\text{Iodofenil}]-3-metilpentadecanoico

preparacion farmaceutica radiactiva

\[\text{C}_{22}\text{H}_{35}\text{I}^{123}\text{O}_2\]

123748-56-1

\[
\begin{align*}
\text{H} & \text{CH}_3 \\
\text{CO}_2\text{H} & \\
& \text{and enantiomer} \\
& \text{et énantiomère} \\
& \text{y enantiómero}
\end{align*}
\]

acidinii bromidum

acidinium bromide

\((3R)-3-\{(\text{hydroxy})\text{di}(\text{thiophen-2-yl})\text{acetyloxy}\}-1-(3\text{-phenoxypropyl})-1,5\text{-azabicyclo}[2.2.2]octan-1-ium bromide
\)

muscarinic receptor antagonist

bromure d'acidinium

bromure de (3R)-3-\{(\text{hydroxybis}(\text{thiophén-2-yl})\text{acétyl})\}-1-\{(3\text{-phénoxypropyl})-1\text{-azoniabicyclo}[2.2.2]oc téane

antagoniste des récepteurs muscariniques

bromuro de acidinio

bromuro de (3R)-1-(3-fenoxipropil)-3-\{(\text{hidroxi})\text{di}(\text{tifen-2-il})\text{acetiloxi})\}-1,5\text{-azabiciclo}[2.2.2]octan-1-ilio

antagonista de los receptores muscarinicos

\[\text{C}_{26}\text{H}_{30}\text{Br}_2\text{NO}_4\text{S}_2\]

320345-99-1
afimoxifenum
afimoxifene
afimoxifène
afimoxifeno
4-(1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenylbut-1-enyl)phenol
antiestrogen
afimoxifène 4-[1-[4-[2-(diméthylamino)éthoxy]phényl]-2-phénylbut-1-ényl]phénol
antioestrogène
afimoxifeno 4-[1-[4-[2-(dimetilamino)etoxi]fenil]-2-fenilbut-1-enil]fenol
antiestrógeno
\[
C_{26}H_{29}NO_2
\]
68392-35-8

afiblerceptum*
aflibercept
daflibercept des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 C-terminal residues)-peptide (Fc fragment), (211-211':214-214')-bisdisulfide
dimer
angiogenesis inhibitor
afiblercept (211-211':214-214')-bisdisulfure du dimère de la dès-432-lisine-
[récepteur 1 humain du facteur de croissance endothélial vasculaire-
(103-204)-peptide (contenant le domaine Ig-like C2-type 2) protéine
de fusion avec le récepteur 2 humain du facteur de croissance
endothélial vasculaire-(206-308)-peptide (contenant un fragment du
domaine Ig-like C2-type 3) protéine de fusion avec
l’immunoglobuline G1 humaine-(227 résidus C-terminaux)-peptide
(fragment Fc)]
inhibiteur de l’angiogénèse
afiblercept
(211-211':214-214')-bisdisulfuro del dímero de la des-432-lisina-
[receptor 1 humano del factor de crecimiento endotelial vascular-
(103-204)-péptido (que contiene el dominio Ig-like C2-tipo 2)
proteína de fusión con el receptor 2 humano del factor de
crecimiento endotelial vascular-(206-308)-péptido (que contiene un
fragmento del dominio Ig-like C2-tipo 3) proteína de fusión con la
inmunoglobulina G1 humana-(227 restos C-terminales)-péptido
(fragmento Fc)]
inhibidor de la angiogénesis
C 4318H6788N1164O1304S32

Monomer / Monomère / Monómero
SDTGRPFVEM
YSEIPEIIHM
TEGRLELIPC
RVTSPNITVT
LKKFPLDTLI
50
PDGKRIIWDS
RKGFIISNAT
YKEIGLLTCE
ATVNGHLYKT
NYLTHRQTNT
100
IIDVVLSPSH
GIELSVGEKL
VLNCTARTEL
NVGIDFNWEY
PSSKHQHKKL
150
VNRDLKTQSG
SEMKKFLSTL
TIDGVTRSDQ
GLYKVAASEG
LHKEKISTFV
200
RVNEDKHTHT
CCPCAPPELL
GGPDVLFPFF
KKRTDLWIER
TVTYCVVVV
250
VHSHEDKUF
NNYCGGRTC
NATKFPEEQ
YSGTYFYVAV
LVTLQGDMIL
300
GEKRYCKVSN
KALAPVTEKK
IESAKQQRRE
PQYTLPFFER
DELTKQKQEL
350
TCILKQYFSP
DIAMENESNG
QYDNPVFQFF
PVLOEDGQFF
LYSKLTVKCI
400
RWWQCNVYFC
SYMMELAHSH
YTQKSLSSLP
G
431

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
30-79 30'-79'
124-185 124'-185'
211-211' 214-214
246-306 246'-306'
352-410 352'-410'

aleglitazarum
aleglitazar
(2S)-2-methoxy-3-[4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1-benzothiophen-7-yl]propanoic acid
antidiabetic

aiëglitazar
acide (2S)-2-méthoxy-3-[4-[2-(5-méthyl-2-phényl-1,3-oxazol-4-yl)éthoxy]-1-benzothiophén-7-yl]propanoïque
antidiabétique

aleglitazar
ácido (2S)-3-[4-[2-(2-fenil-1,3-oxazol-5-metil-4-il)etoxi]-1-benzotiofen-7-il]-2-metoxipropanoico
hipoglucemiante

C 24H23NO5S

475479-34-6

alferminogenum tadenovecum*
alferminogene tadenovec
Recombinant human adenovirus 5 (replication-deficient, E1-deleted) containing a human fibroblast growth factor-4 cDNA sequence driven by a cytomegalovirus promoter
gene therapy product - stimulates angiogenesis

alferminogène tadenovec
adénovirus 5 humain recombinant (réplication-déficient, région E1-supprimée) contenant la séquence ADN-copie du facteur 4 de croissance du fibroblaste humain sous contrôle d’un promoteur de cytomegalovirus
produit de thérapie génique stimulateur de l’angiogénèse

alferminogén tadenovec
adenovirus 5 humano recombinante (replicación-deficiente, con delección E1) que contiene la secuencia DNA-copia del factor-4 de crecimiento de fibroblastos humanos controlado por un promotor de citomegalovirus
producto para genoterapia,estimulante de la angiogénesis

473553-86-5
apilimodum
apilimod 1-[(3-methylphenyl)methylidene]-2-{6-(morpholin-4-yl)-2-[2-(pyridin-2-y1)ethoxy]pyrimidin-4-y1}hydrazine
immunomodulator

apilimod 1-(3-méthylbenzylidène)-2-[6-(morpholin-4-yl)-2-[2-(pyridin-2-y1)éthoxy]pyrimidin-4-yldiazane
immunomodulateur

apilimod 1-(3-metilbencilideno)-2-[6-(morfolin-4-il)-2-[2-(piridin-2-il)etoxi]pirimidin-4-il]diazano
inmunomodulador

C_{23}H_{26}N_{6}O_{2} 541550-19-0

apricitabinum
apricitabine 4-amino-1-[(2R,4R)-2-(hydroxymethyl)-1,3-oxathiolan-4-y1]pyrimidin-2(1H)-one
antiviral

apricitabine (-)-4-amino-1-[(2R,4R)-2-(hydroxyméthyl)-1,3-oxathiolan-4-yl]=pyrimidin-2(1H)-one
antiviral

apricitabina (-)-4-amino-1-[(2R,4R)-2-(hidroximetil)-1,3-oxatiolan-4-il]pirimidin-2(1H)-ona
antiviral

C_{8}H_{11}N_{3}O_{3}S 160707-69-7

atasiceptum*
ataciept [86-serine,101-glutamic acid,196-serine,197-serine,222-aspartic acid,224-leucine]human tumor necrosis factor receptor superfamily member 13B-(30-110)-peptide (TACI fragment containing TNFR-Cys 1 and TNFR-Cys 2) fusion protein with human immunoglobulin G1-(232 C-terminal residues)-peptide (γ1-chain Fc fragment), (92-92':95-95')-bisdisulfide dimer
immunomodulator
atacicept (92-92'•95-95')-bisdisulfure du dimère de la [86-sérine,101-acide glutamique,196-sérine,197-sérine,222-acide aspartique,224-leucine]-protéine de fusion du membre 13B humain de la superfamille des récepteurs du facteur de nécrose tumorale-(30-110)-peptide (portion du TACI incluant les deux régions riches en cystéine) avec l’immunoglobuline G1 humaine-(232 résidus C-terminaux)-peptide (fragment Fc de la chaîne γ1) immunomodulateur

atacicept (92-92'•95-95')-bisdisulfuro del dímero de la [86-serina,101-ácido glutámico,196-serina,197-serina,222-ácido aspártico,224-leucina]-proteína de fusión del miembro 13B humano de la superfamilia de receptores del factor de necrosis tumoral-(30-110)-péptido (porción del TACI que incluye las dos regiones ricas en cisteína) con la inmunoglobulina G1 humana-(232 restos C-terminales)-péptido (fragmento Fc de la cadena γ1) inmunomodulador

C_{116}H_{178}N_{856}O_{950}S_{44} 845264-92-8

Monomer / Monomère / Monómero

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

azilsartanum

azilsartan

2-éthoxy-1-[(2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-yl)methyl]-1H-benzimidazole-7-carboxylic acid angiotensin II receptor antagonist

azilsartan

acide 2-éthoxy-1-[(2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphényl-4-yl)méthyl]-1H-benzimidazole-7-carboxylique antagoniste du récepteur de l’angiotensine II

azilsartán

ácido 2-etoxi-1-[(2'-(5-oxo-4,5-dihidro-1,2,4-oxadioloz-3-il)bifenil-4-il)métil]-1H-bencimidazol-7-carboxílico antagonista del receptor de la angiotensina II

C_{29}H_{32}N_{10}O_{3} 147403-03-0
bavituximab*  

**bavituximab**  

immunoglobulin G1, anti-(phosphatidylserine) chimeric monoclonal ch3G4; gamma1 heavy chain (*Mus musculus* V-Homo sapiens *IGHG1*) (223-214')-disulfide with kappa light chain (*Mus musculus* V-KAPPA-*Homo sapiens* *IGKC*); (229-229''-232-232'')-bisdisulfide dimer antineoplastic

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Formula</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{6446}H_{9946}N_{1702}O_{2042}S_{42}</td>
<td>648904-28-3</td>
<td></td>
</tr>
</tbody>
</table>

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

EVQLQQSGPE EVKLPGASVKL SCKASGYSFT GYNMNWVKQS HGKSLEWIGH 50  

IDPYYGDTSY NQKFRGKATL TDNPSSTAY MQQLSTKDSS SAVYVCYKGG 100  

YSGMYWTYVQ GAGTTTVTSS ASTQGDSVFP LAPSSTKTIGL TAAAGCULY 150  

DYFPPFVTGS NSNIAGLTSV NTPAALVSQG GLSSLPSVTV VPSHLGTQY 200  

VICNVKREPS NTTFQKVKEP KSCDTHTCP PCPAPELLLG PSVPFFPYP 250  

KEDLM13RTT EVTVCVVIVQS HEDPEVFNN YUDGEVNA KTEFPIEYQ 300  

STTVVSVSLL VLQQDNLGC ERVCVSNRA LAPIERTIS KARQFREIQ 350  

VTTLPPRSHOE LTVQVI7LTC LVEGFYPSDI AVENKSSQP ENNYTPFPY 400  

LSDGSFFFLYS SKTVDSHRN QQQNFSCSV MHEALNHTY QC6SLLSQCH 450  

**k Chain / Chaîne k / Cadena k**

DIQMTQSPSS LSASLQEVVS LTCEAQGQIQ S31MLQQOG DQIJAEQ 90  

TEIIGQGPVR RPFGGGEGD YETISLSEL EPKVVCLAQ VQSSPFFPA 100  

GKKELRDAR APEVVFVFPP SDEQLSSTGT SAVCVLNNFY PREAVQWMU 150  

DAMLQGIESQ EVTVQKVDDK STLYFSLTL LSKAYVKRM YVACEVTHQ 200  

LSSPVTKSFN REGC 214

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

bedoradrinum  

**bedoradrine**  

2-[[[(7S)-7-[[[(2R)-2-hydroxy-2-[[4-hydroxy-3-[[2-hydroxyethyl][phenyl]ethyamino-5,6,7,8-tetrahydrodronaphthalen-2-yl]oxy]-N,N-dimethylacetamide β_{1}-adrenoceptor agonist

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Formula</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{6446}H_{9946}N_{1702}O_{2042}S_{42}</td>
<td>648904-28-3</td>
<td></td>
</tr>
</tbody>
</table>

**béдорадрин**  

(-)-2-[[[(7S)-7-[[[(2R)-2-hydroxy-2-[[4-hydroxy-3-[[2-hydroxyethyl][phenyl]ethylamino-5,6,7,8-tetrahydrodronaphthalen-2-yl]oxy]-N,N-diméthylacétamide agoniste β_{1}-adrénergique

<table>
<thead>
<tr>
<th>Chemical Structure</th>
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<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{6446}H_{9946}N_{1702}O_{2042}S_{42}</td>
<td>648904-28-3</td>
<td></td>
</tr>
</tbody>
</table>

**bedoradrina**  

(-)-2-[[[(7S)-7-[[[(2R)-2-hidroxi-2-[[4-hidroxi-3-[[2-hidroxietil][fenil][etil]amino-5,6,7,8-tetrahidronaftalen-2-il]oxy]-N,N-dimetilacetamida agonista del adrenoreceptor β_{1}
**beperminogenum perplasmidum***

beperminogene perplasmid

Plasmid DNA containing human hepatocyte growth factor cDNA sequence driven by a cytomegalovirus promoter
gene therapy product - stimulates angiogenesis for tissue repair

béperminogène perplasme

ADN plasmidique contenant la séquence ADN-copie du facteur de croissance de l'hépatocyte humain sous contrôle d'un promoteur de cytomegalovirus
produit de thérapie génique, stimulateur de l'angiogénèse

beperminógén perplásmido

DNA de plásmido que contiene la secuencia DNA-copia del factor de crecimiento del hepatocito humano controlado por un promotor de citomegalovirus
producto para genoterapia, reparador tisular estimulante de la angiogénesis

---

**beroctocogum alfa***

beroctocog alfa

human blood-coagulation factor VIII-(1-740)-peptide complex with human blood-coagulation factor VIII-(1649-2332)-peptide
blood coagulation factor

béroctocog alfa

combinaison du facteur VIII de coagulation humain-(1-740)-peptide (chaîne lourde du facteur VIIIa, isoforme de 92 kDa) avec le facteur VIII de coagulation humain-(1649-2332)-peptide (chaîne légère du facteur VIIIa)
facteur de coagulation sanguine/antihémophilique

beroctocog alfa

combinación del factor VIII de coagulación humano-(1-740)-péptido (cadena pesada del factor VIIIa, isoforma de 92 kDa) con el factor VIII de coagulación humano-(1649-2332)-péptido (cadena ligera del factor VIIIa)
factor de coagulación sanguínea
Proposed INN: List 95


Heavy chain / Chaîne lourde / Cadena pesada

ATRVYGLAG ELONIVMGEC LGELFYDQSF PRVPRMLPF NTVVYKRKL 50
FVEVTDDLFP IAKRPRRMGE LLQGTTQAEV YSTDVTLMK MASHPVISLA 100
VYQYVQMAKA GAEYVQQTQ SGKEDVRVFF GQGSTTVQW LEKQGPAID 150
PLCITYSLYS HYFLVQLENS GLGAPQLCRC ESLQASERTQ TLKHFLLLE 200
VSIEGSSRHS ERYQSLAQQR DASAARAKPK MTRVNGYVR SLGGLIGCR 250
KXVYVQIVCM GTFPVEYIF SFLECHLYVRN HQQALIEIFP LFTYLATLIL 300
MDIQVLLLPC HISSRQGHR EAYKVRSDCP KEEQLEKNEEN EAEADDYYDL 350
TSGMOMQVRQ CDEHSPSFAQ IRSVAKKRPK TRVYITAASSK IDMOAYFYL 400
APFDTRYSQK YLNNHQGQR RIKYKVRFMA YTDQFRTKE AIQHEGSLIL 450
FILYQEGVDV LLLIFERQAG RPYTVPHQG TDVAVLIEHR LPGQVIFLLK 500
FPVQGEIFS FKYTVTVSFQ PTSDKPRCLT KYQSFVNYNE RDLASGILCH 550
LILITKRESVD QGNQIMQDQ RNHFLPSYVD ERKSWYLTEN IQRFLPNFAG 600
VQLEDPEFGA SNNHSGISNY VFSDQSLCSV LWHTAVWIL SIGAQTFPLS 650
VFVSSCTFKH KMVEYDTLIL FFPSGTVFMH SMENPGWIL GCHMDFNNR 700
GMTALLKVES CIKNTGQYVE DSTISEDASYL LKNNMTAIF S 741

Light chain / Chaîne légère / Cadena ligera

EI 1650
TRTTLQSDQE EISDGDTSVE EMKEKDFCHY DEDENQSPSFQ FKQKTQRYFI 1700
AIVERLMOCY MGSSPRLANR RAGQSGYPQF KRYKQVQPED GTFQYLRG 1750
ELNEHLLGIG PYRAKVEQDN INVTRFQKAS RPVSFTVSLI SYFESDRQCA 1800
ESKPNVYKVN ETXTPVQWQX HMQARTKDPF DCMAYVYDSED VOLEKHDNG 1850
LIGQPLVCNT NTLANHABCQ VTVQEFALLFF TIPDETSKLY FTRMHEHNC 1900
APCHQMDGIP TFKENYKPHA INGYIMDTLFL GLYMQAQDRQI KNYLLGQHNS 1950
ENHISHERFG HVFTYKRKEEK YGALKLNLTP GPVETFMLPSQ SLAGREVEC 2000
LIGEHQAMLK STLTVQSCPQ CNQPLCMASG HIRQFQGTAS TQGQWAKRP 2050
ARLYQSCIN AMSTKEFQAM ITQVULAPFI IINGTQGQAR QKFQSLYSQ 2100
FPMWILSCNY KNYQYGRSVT GTLQFVFQNH DSCGQDMNF NPQIASSYVR 2150
LFKRTYSAIR LTELQGAMCD LMCSNPLGHN EKSAIGAQQ TASSYTFMNP 2200
ATKPSKRLMK HQQRSNARQH FQVMENXIL YQGQWTQVSH TOQVQVQES 2250
FLSTENVKPK LIISSQDHGQWTLQFQQNVS QKVQFRQDGQF TVVWISLLOP 2300
LLNTRSLHMF QSIVQACLRW MEVLCIQAQY LG 2332

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

Glycosylation sites / Sites de glycosylation / Posiciones de glicosilación

Modifications / Modificaciones

Y = 4-O-sulfotyrosyl

bremelanotidum

bremelanotide

2,7-anhydro(N-acetyl-L-2-aminohecanoyl-L-aspartyl-L-histidyl-D-phenylalanyl-L-arginyl-L-tryptophyl-L-lysine)

melanocortin receptor agonist

brémelanotide

N-acétyl-L-2-aminohecanoyl-L-α-aspartyl-L-histidyl-D-phénylalanyl-L-arginyl-L-tryptophyl-L-lysine-(2→7)-lactame

agoniste du récepteur de la mélanocortine

bremelanotida

N-acetil-L-2-aminohecanoil-L-α-aspartil-L-histidil-D-fenilalanil-L-arginiil-L-triptofili-L-lisina-(2→7)-lactama

agonista del receptor de la melanocortina

124
**bucelipasum alfa**
bucelipase alfa

human bile-salt-activated lipase (cholesterol esterase, EC 3.1.1.13), glycoform alfa (recombinant hBSSL) enzyme

**bucélipase alfa**
lipase activée par les sels biliaires humaine (cholestérol estérase, EC 3.1.1.13), glycoforme alpha (recombinante hBSSL) enzyme

**bucelipasa alfa**
lipasa humana activada por las sales biliares (colesterol esterasa, EC 3.1.1.13), glicoforma alfa (recombinante hBSSL) enzima

C<sub>343</sub>H<sub>525</sub>N<sub>894</sub>O<sub>1041</sub>S<sub>17</sub> 9026-00-0

**camobucolum**
camobucol

4-{4-[1-[3,5-di-tert-butyl-4-hydroxyphenyl]sulfanyl]propan-2-yl}= sulfanyl]-2,6-di-tert-butylphenoxy]acetic acid anti-inflammatory

**camobucol**

ácido 4-{4-[1-[3,5-bis(1,1-diméthyléthyl)-4-hydroxyfenil]sulfanil]-1-méthyléthyl]sulfanil}-2,6-bis(1,1-diméthyléthyl)phénox_saida acética anti-inflamatoire

**camobucol**

ácido 4-{4-[2-(3,5-di-terc-butil-4-hidroxifenil)sulfanil]propan-2-il}= sulfanil]-2,6-di-terc-butifenoxo]ácetico antiinflamatorio

C<sub>33</sub>H<sub>50</sub>O<sub>4</sub>S<sub>2</sub> 216167-92-9

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

Glycosylation sites / Sites de glycosylation / Posiciones de glicosilación

Aaa-187 Thr-538 Thr-642 Thr-576 Thr-587
Thr-598 Thr-609 Thr-620 Thr-631

125
capadenosonum

2-amino-6-[((2-(4-chlorophenyl)-1,3-thiazol-4-yl)methyl)sulfanyl]-4-[4-(2-hydroxyethoxy)phenyl]pyridine-3,5-dicarbonitrile
adenosine A1 receptor agonist

C_{25}H_{18}ClN_{5}O_{2}S_{2}  54417-40-5

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catramilastum

1-{(2S)-2-[3-(cyclopropylmethoxy)-4-methoxyphenyl]propyl}-1,3-dihydro-2H-imidazol-2-one
phosphodiesterase IV inhibitor

C_{17}H_{22}N_{2}O_{3}  183659-72-5

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cediranibum

4-{(4-fluoro-2-methyl-1H-indol-5-yl)oxy}-6-methoxy-7-[3-(pyrrolidin-1-yl)propoxy]quinoxaline
angiogenesis inhibitor

C_{26}H_{26}ClN_{5}O_{4}S  163578-84-0
denibulinum

denibulin
methyl [5-[(4-[2S]-2-aminopropanamido)phenyl]sulfanyl]-1H-benzimidazol-2-yl]carbamate
antineoplastic

dénibuline
[5-[(4-[2S]-2-aminopropanamido)phenyl]sulfanyl]-1H-benzimidazol-2-yl]carbamate de méthyle
antineoplasique

denibulina
[5-[(4-[2S]-2-aminopropanamido)fenil]sulfanil]-1H-bencimidazol-2-il]carbamato de metilo
antineoplásico

dexelvucitabinum

dexelvucitabine
4-amino-5-fluoro-1-[(2R,5S)-5-(hydroxymethyl)-2,5-dihydrouran-2-yl]pyrimidin-2(1H)-one
antiviral

dexelvucitabine
(+)-4-amino-5-fluoro-1-[(2R,5S)-5-(hydroxyméthyl)-2,5-dihydrouran-2-yl]pyrimidin-2(1H)-one
antiviral

dexelvucitabina
(+)-4-amino-5-fluoro-1-[(2R,5S)-5-(hidroximetil)-2,5-dihidrouran-2-il]pirimidin-2(1H)-ona
antiviral

C_{25}H_{27}FN_{4}O_{3} 288383-20-0

C_{18}H_{19}N_{5}O_{3}S 284019-34-7

C_{9}H_{10}FN_{3}O_{3} 134379-77-4
efungumab*  

**efungumab**  
immunoglobulin scFv fragment, anti-(heat shock protein 90 homolog from *Candida albicans* (yeast)), methionylalanyl-[human monoclonal HSP90mab VH domain (120 residues)]-tris[tetraglycyl]-seryl-[human monoclonal HSP90mab V-KAPPA domain (107 residues)]-[arginyl-trialanyl-leucyl-glutamyl]-hexahistidine immunomodulator

éfungumab  
immunoglobuline fragment scFv, anti-(homologue de la protéine de choc thermique 90 de *Candida albicans* (levure)), methionylalanyl-[domaine VH (120 résidus) de l'anticorps monoclonal humain HSP90mab]-tris[tetraglycyl]-seryl-[domaine V-KAPPA (107 résidus) de l'anticorps monoclonal humain HSP90mab]-[arginyl-trialanyl-leucyl-glutamyl]-hexahistidine immunomodulateur

efungumab  
immunoglobulina fragmento scFv, anti-(homólogo de la proteína de choc térmico 90 de *Candida albicans*), metionilalanil-[dominio VH (120 restos) del anticuerpo monoclonal humano HSP90mab]-tris[tetraglicil]-seryl-[dominio V-KAPPA (107 restos) del anticuerpo monoclonal humano HSP90mab]-[arginil-trialanil-leucil-glutamil]-hexahistidina immunomodulador

762260-74-2

MAEVQVLVES GAEVKKPGES LRISCKGSGC IISSYWISWV RQMPGKGLEW MGKIDFGGSY INYSPFQGH VSIGDKNSIN TAYLQWNSLA ASDTAMYYCA MKGRPFDDSF SYMQQQTLTV VHSGGGGSGG GGGGGSVD GNTQEPSFLS APYQGDRITIT CRAISSISRY LAWQGQAPK AKFLLAAAA TLDQVESBF GSGGSQETE PTINQLQPEL FATYYQHLN SYPLFTGGSV KVDKRAAA LEHHHHH

elacytarabine  

**elacytarabine**  
4-amino-1-{(5-O-[{9E}-octadec-9-enoyl]-β-D-arabinofuranosyl]=pyrimidin-2(1H)-one antineoplastic

élacytarabine  
4-amino-1-{(5-O-{(9E)-octadéc-9-énoyl]}-[D-arabinofuranosyl]=pyrimidin-2(1H)-one antinéoplasique

elacitarabina  
4-amino-1-{(5-O-[(9E)-octadec-9-enol]}-[β-D-arabinofuranosil]pirimidin-2(1H)-ona antineoplásico

C_{27}H_{45}N_{3}O_{6}  

188181-42-2

[Chemical structure diagram]
elocalcitolum
elocalcitol

\((1S,3R,5Z,7E,23E)\)-1-fluoro-26,27-dihomo-9,10-secocholesta-5,7,10(19),16,23-pentaene-3,25-diol
vitamin D analogue

intégralcalcitol
intégralcitol

\((1R,5S)-3-[(1Z)-2-[(3aS,4E,7aS)-1-[(1S,3E)-5-éthyl-5-hydroxy-1-méthylhept-3-ényl]-7a-méthyl-3,3a,5,6,7,7a-hexahydro-4H-indén-4-yliénié][éthylidénié]-5-fluoro-4-méthyliéne cyclohexanol
analog de la vitamine D

elocalcitolum
elocalcitol

\((1S,3R,5Z,7E,23E)\)-1-fluoro-26,27-dihomo-9,10-secocholesta-5,7,10(19),16,23-pentaene-3,25-diol
análogo de la vitamina D

C\(_{29}\)H\(_{43}\)FO\(_2\) 199798-84-0

elsibucolum
elsibucol

4-{4-[(2-[[3,5-di-tert-butyl-4-hydroxyphenyl]sulfanyl]propan-2-yl]sulfanyl}-2,6-di-tert-butylphenoxy}butanoic acid
anti-inflammatory

elsibucol
acide 4-[4-[[1-[3,5-bis(1,1-diméthyléthyl)-4-hydroxyphényl]sulfanyl]-1-méthyléthyl]sulfanyl]-2,6-bis(1,1-diméthyléthyl)phénoxy}butanoïque
anti-inflammatoire

elsibucol
ácido 4-{4-[(2-[3,5-di-terc-butil-4-hidroxifenil]sulfanil]propan-2-il]sulfanil}-2,6-di-terc-butilfenoxi}butanoico
antinfiamatorio

C\(_{35}\)H\(_{54}\)O\(_4\)S\(_2\) 216167-95-2
**epoetinum theta**
epoetin theta

human erythropoietin-(1-165)-peptide, glycoform θ
antianaemic

**époétine thêta**
erythropoïétine humaine-(1-165)-peptide, glycoforme θ
antianémique

**epoetina zeta**
eritropoyetina humana-péptido-(1-165), glicofomna θ
antianémico

C₈₀₉H₁₃₀₁N₂₂₉O₂₄₀S₅ 762263-14-9

**ferroquinum**
ferroquine

N’-(7-chloroquinolin-4-yl)-N,N-dimethyl-C,C’-(ferrocene-1,2-diyl)=dimethanamine
antimalarial

ferroquine

N’-(7-chloroquinoléin-4-yl)-N,N-diméthyl-C,C’-(férrocène-1,2-diyl)=diméthanamine
antipaludique

ferroquina

N’-(7-cloroquinolin-4-il)-N,N-dimetil-C,C’-(ferroceno-1,2-diil)=dimetanamina
antipalúdico

C₂₃H₂₄ClFeN₃ 185055-67-8

**fluticasonum furoas**
fluticasone furoate

6α,9-difluoro-17-[[fluorométhyl)sulfanyl]carbonyle]-11β-hydroxy-16α-méthyl-3-oxyandrosta-1,4-dièn-17α-yl furane-2-carboxylate
steroidal anti-inflammatory

furane-2-carboxylate de 6α,9-difluoro-17-[[fluorometil)sulfanil]carbonyle]-11β-hidroxi-16α-metil-3-oxyandrosta-1,4-dièn-17α-yle
ant-inflammatoire stéroidien

furano-2-carboxiatle de 6α,9-difluoro-17-[[fluorometil)sulfanil]carbonyle]-11β-hidroxi-16α-metil-3-oxyandrosta-1,4-dièn-17α-ilo
corticosteroid antiinflamatorio
fosalvudinum tidoxilum
fosalvudine tidoxil
(2RS)-2-(decyloxy)-3-[(dodecyl)sulfinyl]propyl [(2R,5S,5R)-3-fluoro-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl]methyl hydrogen phosphate
antiviral

fosalvudine tidoxil
hydrogénotrophosphate de (2RS)-2-(décylexy)-3-(dodécylsulfanil)propyle et de [(2R,5S,5R)-3-fluoro-5-(5-méthyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tétrahydrofuran-2-yl]méthyle
antiviral

fosalvudina tidoxilo
hidrógenofosfato de (2RS)-2-(deciloxi)-3-[(dodecil)sulfanil]propilo y [(2R,5S,5R)-3-fluoro-5-(5-metil-2,4-dioxo-3,4-dihidropirimidin-1(2H)-il)tetrahidrofuran-2-il]metilo
antiviral

Gamithromycinum
Gamithromycin
(2R,3S,4R,5S,8R,10R,11R,12S,13S,14R)-13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihidroxy-3,5,8,10,12,14-hexametil-7-propil-11-[(3,4,6-trideoxy-3-(dimetilamino)-β-D-xylo-hexopyranosyl)oxy]-1-oxa-7-azacyclopentadecan-15-one
antibiotic (veterinary use)

Gamithromycin
(2R,3S,4R,5S,8R,10R,11R,12S,13S,14R)-13-[(2,8-didésoxy-3-C-méthyl-3-O-méthyl-α-L-ribo-hexopyranosyl)oxy]-2-éthyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexaméthyl-7-propyle-11-[(3,4,6-tridésoxy-3-(diméthylamino)-β-D-xyl-hexopyranosyl)oxy]-1-oxa-7-azacyclpentadécén-15-one
antibiotique (usage vétérinaire)

Gamitromicina
Gamitromicina
antibiótico de uso veterinario
ilepatrilum

ilepatril

(4S,7S,12bR)-7-[[2S]-2-(acetylsulfanyl)-3-methylbutanamido]-6-oxo-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]benzazepine-4-carboxylic acid antihypertensive

ilépatril

acide (4S,7S,12bR)-7-[[[2S]-2-(acétylsulfanyl)-3-méthylbutanoïl]-amino]-6-oxo-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]= benzazépine-4-carboxylque antihypertenseur

ilepatriló

ácido (4S,7S,12bR)-7-[[[2S]-2-(acetilsulfanil)-3-metilbutanoil]amino]-6-oxo-1,2,3,4,6,7,8,12b-octahidropirido[2,1-a][2]benzazepina-4-carboxílico antihipertensivo

C₉₈H₇₆N₂O₁₂  145435-72-9

imisopasemum manganum

imisopasem manganese

(PBPY-7-11-2344'3')-dichloro[(4aR,13aR,17aR,21aR)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17a,18,19,20,21,21a-icosahydro-7,11-(azeno)dibenzo[b,h][1,4,7,10]= tetraazacycloheptadencine-κ⁴N⁺,N⁵⁺,N¹³⁺,N¹⁸⁺,N²¹⁺,N²²⁺]manganese anti-inflammatory

imisopasem manganése

(PBPY-7-11-2344'3')-dichloro[(4aR,13aR,17aR,21aR)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17a,18,19,20,21,21a-icosahydro-11,7-nitriolo-7H-dibenzo[b,h][1,4,7,10]= tétéraazacycloheptadécine-κ⁴N⁺, κN³⁺, κN⁸⁺, κN¹³⁺, κN¹⁸⁺, κN²¹⁺, κN²²⁺]manganése anti-inflammatoire

C₂₂H₂₈N₂O₅S  473289-62-2
Proposed INN: List 95

**Imisopasem manganoso**

\[
(PBPY-7-11-2344'3')-dichloro\{(4aR,13aR,17aR,21aR)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17a,18,19,20,21,21a-icosahidro-7,11-(azeno)dibenzo[6,7][1,4,7,10]-
tetraazacicloheptadecin-κ^2N^3,N^4,N^14,N^15,N^16,N^17\}manganos
antinflamatorio
\]

C_{21}H_{35}Cl_{2}MnN_{5} 218791-21-0

**Inakalantum**

**Inakalant**

tert-butyl (2-\{7->(2S)-3-(4-cyanophenoxy)-2-hydroxypropyl\}-9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl\}ethyl\}carbamate

antiarrhythmic

\[
(2\{7->(2S)-3-(4-cianofenoxi)-2-hidroxipropil\}-9-oxa,3,7-diazabiciclo=\[3.3.1]non-3-il\}etil\}carbamato de terc-butilo
\]

antiarritmico

C_{23}H_{34}N_{4}O_{5} 335619-18-6

**Lapaquistatum**

**Lapaquista**

(1->(3R,5S)-1-[3-(acetyloxy)-2,2-dimethylpropil]\}-7-chloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl\}acetyl\}piperidin-4-yl\}acetic acid

squalene synthase inhibitor

\[
[1-[(3R,5S)-1-3-(acetiloxi)-2,2-dimetilpropil]\}-7-chloro-
5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazépin-
3-yl\}acétyl\}pipéridin-4-yl\}acétique
\]

inhibiteur de la squalème synthétase

\[
[1-[(3R,5S)-1-3-acetiloxi)-2,2-dimetilpropil]\}-7-cloro-
5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-
3-il\}acetil\}piperidin-4-il\}acético
\]

inhibidor de la escualeno sintetasa
levonadifloxacincum  
levonadifloxacín  
(5S)-9-fluoro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-6,7-dihydro-1H,5H-benzo[j]quinolizine-2-carboxylic acid antibacterial

lévonadifloxacine  
(-)-acide (5S)-9-fluoro-8-(4-hydroxypipéridin-1-yl)-5-méthyl-1-oxo-6,7-dihydro-1H,5H-benzo[j]quinolizine-2-carboxylique antibactérien

levonadifloxacino  
ácido (5S)-9-fluoro-8-(4-hidroxipiperidin-1-il)-5-metil-1-oxo-6,7-dihidro-1H,5H-benzo[j]quinolizina-2-carboxílico antibacteriano

C₁₉H₂₁FN₂O₄  
154357-42-3

exatumumabum*  
exatumumab  
immunoglobulin G1, anti-[human tumor necrosis factor receptor superfamily member 10B (TNFRSF10B, death receptor 5, TNF-related apoptosis-inducing ligand receptor 2, TRAIL-R2, CD262)] human monoclonal HGS-ETR2; gamma1 heavy chain (Homo sapiens VH-IGHG1) (224-213')-disulfide with lambda light chain (Homo sapiens V-LAMBDA- IGLC2); (230-230'':233-233'')-bisdisulfide dimer antineoplastic

exatumumab  
immunoglobuline G1, anti-[membre 10B de la super famille des récepteurs du facteur de nécrose tumorale humain (TNFRSF10B, death receptor 5, TRAIL-R2, CD262)] anticorps monoclonal humain HGS-ETR2; chaîne lourde gamma1 (Homo sapiens VH-IGHG1) (224-213')-disulfure avec la chaîne légère lambda (Homo sapiens V-LAMBDA- IGLC2); dimère (230-230'':233-233'')-bisdisulfure antineoplasique
lexatumumab

immunoglobulina G1, anti-[miembro 10B de la superfamilia de receptores del factor de necrosis tumoral humano (TNFRSF10B, death receptor 5, TRAIL-R2, CD262)] anticuerpo monoclonal humano HGS-ETR2; cadena pesada gamma1 (Homo sapiens V-IGHG1) (224-213')-disulfuro con la cadena ligera lambda (Homo sapiens V-LAMDA- IGLC2); dimero (230-230'"233-233")-bisdisulfuro

antineoplásico

C_{636}H_{932}N_{172}O_{200}S_{42}

845816-02-6

Heavy chain / chaîne lourde / cadena pesada

EVQLVQSGGGL YRHPGSGDFL SSARRGRFTVS VQNYKMTVSR DYGMSWVRQA PGKGLEWVSG

INWGGTQFTY ADSPQKTVTV QNBRNSLPA KDHVYCAKL

GAGGRHYTOL WQKGTTPVTV SASTKPGSFL PLAPSEKSTS GOTAALGCLV

KUYPFEPYTVTN SNKGAQIIQG VNTPFAVLQS SOLVLESSLV TFPOSELGHQ

TYTCNVNREK SNTRVCRKRE PKSCDHNTLC FCPASELGG GSPYFLLFFP

FQYLMHSTF PEYCYTVDDQ SHDREWKNF RTVCOVKYN AKTFRQPHP

HEYFVQVSL YIVLSQMEIL QKRYCQVNEK ALPAPISRTI SHRAQYQEP

QYuTLPSRE ENTMKVQSL2 CLVKGFPYSSGIAVREKSHQ PENNYFSTFP

VLDSSQGTLF NVKLVQKSH WQGQMYFSCS VRHEALSHNY TVKQSLLSF

Lambda chain / chaîne lambda / cadena ligera

SSELQQLFQAV SVALGSFTRI TCQGDSLAKY YASNQWQKPG QAPVLVIYRG

NNPQGQFPR FGSSQGQAEN SLTITCAQPDE DQAVYCHER DQCHNHVPG

GGKTVLIQV PEAPAFTYLF PPSREIQGQAN KATLVCILDZ FYQAVTIVAN

RAISSVYKAC VETTTFRRQS WRYAXASSV3L SLTVFQKWNK RSQTCQYHRE

GYSVERTVAP TEC5

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

22-96 22'-96' 22''-96'' 22'''-96''' 136'-195' 136'''-195''
22-87 22'-87' 22''-87'' 22'''-87''' 136-195 136'''-195''
213-224 213'-224' 213''-224'' 213'''-224'''

lificiguatum

lificiguat

[5-(1-benzyl-1H-indazol-3-yl)furan-2-yl]methanol

guanylate cyclase activator

lificiguat

[5-(1-benzyl-1H-indazol-3-yl)furan-2-yl]méthanol

activateur de la guanylate cyclase

lificiguat

[5-(1-bencil-1H-indazol-3-il)furan-2-il]metanol

activador de la guanilato ciclasa

C_{19}H_{16}N_{2}O_{2} 170632-47-0

N

N

O

OH
lobeglitazone

\((5RS)-5\{4-\{2-\{6-(4-methoxyphenoxo)pyrimidin-4-y]methylamino=\ethoxy\}phenyl[methyl]-1,3-thiazolidine-2,4-dione\)

antidiabetic

lobégitazone

\((5RS)-5\{4-\{2-\{6-(4-méthoxyphénoxy)pyrimidin-4-y]\mélamino=\éthoxy\}benzyl\}thiazolidine-2,4-dione\)

hypoglycémiant

lobeglitazona

\((5RS)-5\{4-\{2-\{6-(4-metoxifenoxi)pirimidin-4-il]metilamino=\etoxi\}benzil\}tiazolidina-2,4-diona\)

hipoglucemiante

\(\text{C}_{24}\text{H}_{24}\text{N}_{4}\text{O}_{5}\text{S}\)

607723-33-1

lorcaserinum

lorcaserin

\((1R)-8\text{-cloro}-1\text{-methyl}-2,3,4,5\text{-tetrahydro-1H}-3\text{-benzazepine}\)

serotonin receptor agonist

lorcasérine

\((1R)-8\text{-chloro}-1\text{-métyl}-2,3,4,5\text{-tétrahydro-1H}-3\text{-benzazépine}\)

agoniste des récepteurs de la sérotonine

lorcaserina

\((1R)-8\text{-cloro}-1\text{-metil}-2,3,4,5\text{-tetrahidro-1H}-3\text{-benzazepina}\)

agonista del receptor de la serotonina

\(\text{C}_{11}\text{H}_{14}\text{ClN}\)

616202-92-7

mifamurtidum

mifamurtide

\(2\{\{N\{\{2R\}2\}2\}\{2\text{-acetamido-2,3-dideoxy-}d\text{-glucopyranos-3-}\}\}\}\text{oxy}\}=\text{propanoyl}\}1\text{-alanyl-b-isoglutaminy}1\text{-alanyl}\}1\text{amino}1\}1\text{ethyl}\}

(2R)-2,3-bis(hexadecanoyloxy)propyl hydrogen phosphate

antineoplastic

mifamurtide

hydrogénophosphate de 2\{\{N\{\{2R\}-2\}2\}\{3R,4R,5S,6R\}-3\-(acétylamino)-2,5-dihydroxy-6-(hydroxyméthyl)tétrahydro-2H-pyran-4-yloxy\}propanoyl\}1\text{-alanyl-b-isoglutaminy}1\text{-alanyl}1\}1\text{éthyle et de (2R)-2,3-bis(hexanoyloxy)propyle\}

antineoplastique

mifamurtida

hidrógenofosfato de 2\{\{N\{\{2R\}-2\}2\}\{3R,4R,5S,6R\}-3\-(acetilamino)-2,5-dihidroxi-6-(hidroximetil)tetrahidro-2H-piran-4-iloxy\}propanoilo\}1\text{-alalni-b-isoglobutaminy}1\text{-alalni}1\}1\text{etil y de (2R)-2,3-bis(hexanoiloxy)propilo\}

antineopláxico
migalastatum
migalastat
(2R,3S,4R,5S)-2-(hydroxymethyl)piperidine-3,4,5-triol
alpha-galactosidase A enzyme inhibitor

migalastat
(+)-(2R,3S,4R,5S)-2-(hydroxyméthyl)pipéridine-3,4,5-triol
inhibiteur de l’alpha-galactosidase A

migalastat
(2R,3S,4R,5S)-2-(hidroximetil)piperidina-3,4,5-triol
inhibidor de la alfa-galactosidasa A

mirodénafil
mirodénafil
5-éthyl-2-[5-{4-(2-hydroxyéthyl)pipérazin-1-yl}sulfonyl]-
2-propoxyphenyl]-7-propyl-3,5-dihydro-4H-pyrrolo[3,2-d]pyrimidine-
4-one
vasodilatateur

mirodénafil
mirodénafil
5-éthyl-2-[5-{4-(2-hydroxyethyl)piperazin-1-yl}sulfonyl]-
2-propoxyphenyl]-7-propyl-3,5-dihydro-4H-pyrrolo[3,2-d]pyrimidine-
4-one
vasodilatateur

mirodénafilo
mirodénafilo
5-etil-2-[5-{4-(2-hidroxietil)piperezin-1-il}sulfonil]-2-propoxifenil]-
7-propil-3,5-dihidro-4H-pirrolo[3,2-d]pirimidin-4-on
vasodilatador

862189-95-5
motavizumab*  
immunoglobulin G1, anti-(human respiratory syncytial virus glycoprotein F) humanized monoclonal MEDI-524; gamma1 heavy chain [humanized VH \((\text{Homo sapiens FR/Mus musculus CDR})\)-\((\text{Homo sapiens IGHG1})\) (223-213')-disulfide with kappa light chain [humanized V-KAPPA (\((\text{Homo sapiens FR/Mus musculus CDR})\)-\((\text{Homo sapiens IGKC})\) dimère (229-229'-232-232')-bisdisulfide dimer immunomodulator

motavizumab  
immunoglobuline G1, anti-(glycoprotéine de fusion du virus syncytial respiratoire humain) anticorps monoclonal humanisé MEDI-524; chaîne lourde gamma1 [\((\text{VH humanisé (Homo sapiens FR/Mus musculus CDR)})\)-\((\text{IGHG1})\) (223-213')-disulfure avec la chaîne légère kappa [\((\text{V-KAPPA humanisé (Homo sapiens FR/Mus musculus CDR)})\)-\((\text{IGKC})\)] dimère (229-229'-232-232')-bisdisulfure immunomodulateur

motavizumab  
immunoglobulina G1, anti-(glicoproteína de fusión del virus sincitial respiratorio humano) anticuerpo monoclonal humanizado MEDI-524; cadena pesada gamma1 [\((\text{VH humanizada (Homo sapiens FR/Mus musculus CDR)})\)-\((\text{IGHG1})\) (223-213')-disulfuro con la cadena ligera kappa [\((\text{V-KAPPA humanizada (Homo sapiens FR/Mus musculus CDR)})\)-\((\text{IGKC})\)] dimére (229-229'-232-232')-bisdisulfide dimer immunomodulador

\[
\text{C}_{6476}\text{H}_{10014}\text{N}_{1706}\text{O}_{2008}\text{S}_{48}
\]

\[
677010-34-3
\]

naproxcinodum  
4-(nitrooxy)butyl (2S)-2-(6-methoxynaphthalen-2-yl)propanoate  
anti-inflammatory

naproxcinod  
(2S)-2-(6-méthoxynaphtalén-2-yl)propanoate de 4-(nitrooxy)butyle  
anti-inflammatoire

naproxcinod  
(2S)-2-(6-metoxinaftalen-2-il)propanoato de 4-(nitrooxi)butilo  
antiinflamatorio
Proposed INN: List 95

**omtriptolidum**

omtriptolide

4-[[3b,4aS,5aR,6R,6aS,7aS,7bS,8aS,8bS]-8b-methyl-6a-(propan-2-yl)-1-oxo-1,3,3b,4,4a,6,6a,7a,7b,8b,9,10-dodecahydrotrisoxireno[4b,5:6,7:8a,9]phenanthro[1,2-c]furan-6-yl]oxy]-4-oxobutanoic acid

antineoplastic

**omtriptolide**

acide 4-[[3b,4aS,5aR,6R,6aS,7aS,7bS,8aS,8bS]-8b-méthyl-6a-(1-méthylethyl)-1-oxo-1,3,3b,4,4a,6,6a,7a,7b,8b,9,10-dodecahydrotrisoxireno[4b,5:6,7:8a,9]phénanthro[1,2-c]furan-6-yl]oxy]-4-oxobutanoïque

antinéoplasique

**omtriptolida**

ácido 4-[[3b,4aS,5aR,6R,6aS,7aS,7bS,8aS,8bS]-8b-metil-6a-(propan-2-il)-1-oxo-1,3,3b,4,4a,6,6a,7a,7b,8b,9,10-dodecahidrotrisoxireno[4b,5:6,7:8a,9]fenantro[1,2-c]furan-6-il]oxy]-4-oxobutanoico

antineoplásico

**pafuramidinum**

pafuramidine

4,4'-(furan-2,5-diyl)bis(N-methoxybenzenecarboximidamide)

antiparasitic

pafuramidine

4,4'-(furane-2,5-diyl)bis(N-méthoxybenzènecarboximidamide)

antiparasitaire

pafuramidina

4,4'-(furano-2,5-diil)bis(N-metoxibenzenocarboximidama)

antiparásitario

**C_{24}H_{24}O_{9}**

195883-06-8

**C_{18}H_{21}NO_{6}**

163133-43-5

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<th>Chemical</th>
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<tr>
<td>pafuramidinum</td>
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</tbody>
</table>

139
piraxostatum
piraxostat 1-[3-cyano-4-{(2,2-dimethylpropoxy)phenyl}-1H-pyrazole-4-carboxylic acid
xanthine oxidase inhibitor

piraxostat acide 1-[3-cyano-4-{(2,2-dimethylpropoxy)phenyl}-1H-pyrazole-4-carboxylique
inhibiteur de la xanthine oxydase

piraxostat ácido 1-[3-ciano-4-{(2,2-dimetilpropoxi)fenil}-1H-pirazol-4-carboxílico
inhibidor de la xantina oxidasa

C_{16}H_{17}N_{3}O_{3} 206884-98-2

pramiconazolum
pramiconazole 1-{4-{4-[4-{4-{[(2S,4R)-4-(2,4-difluorophenyl)-4-[(1H-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-2-yl]methoxy}phenyl]piperazin-1-yl}phenyl]-3-(propan-2-yl)imidazolidin-2-one
antifungal

pramiconazole (+)-1-{4-{4-[4-{4-{[(2S,4R)-4-(2,4-difluorophényl)-4-[(1H-1,2,4-triazol-1-yl)méthyl]-1,3-dioxolan-2-yl]méthoxy}phényl]pipérazin-1-yl}phényl]-3-(1-méthyléthyl)imidazolidin-2-one
antifongique

pramiconazol 1-{4-{4-{4-[4-{[(2S,4R)-4-(2,4-difluorofenil)-4-[(1H-1,2,4-triazol-1-il)metil]-1,3-dioxolan-2-il]metoxi]fenil]piperazin-1-il}fenil]-3-(propan-2-il)imidazolidin-2-ona
antifúngico

C_{35}H_{39}F_{2}N_{7}O_{4} 219923-85-0

prinaberelum
prinaberel 7-ethenyl-2-(3-fluoro-4-hydroxyphenyl)-1,3-benzoxazol-5-ol
beta estrogen receptor agonist

prinabérel 7-éthényl-2-(3-fluoro-4-hydroxyphényl)-1,3-benzoxazol-5-ol
agoniste des récepteurs oestrogéniques beta

prinaberel 7-etenil-2-(3-fluoro-4-hidroxifenil)-1,3-benzoxazol-5-ol
agonista de los receptores estrogénicos beta
Proposed INN: List 95

rilonaceptum*  
riloncept  
[653-glycine]human interleukin-1 receptor accessory protein-(1-339)-peptide (extracellular domain fragment) fusion protein with human type 1 interleukin-1 receptor-(5-316)-peptide (extracellular domain fragment) fusion protein with human immunoglobulin G1-(229 C-terminal residues)-peptide (Fc fragment)]. (659-659':662-662')-bisdisulfide dimer 
immunomodulator

riloncept  
(659-659':662-662')-bisdisulfure du dimère de la 
[653-glycine]protéine accessoire du récepteur de l’interleukine-1 humaine-(1-339)-peptide (fragment du domaine extracellulaire) protéine de fusion avec le récepteur de type I humain de l’interleukine-1-(5-316)-peptide (fragment du domaine extracellulaire) protéine de fusion avec l’immunoglobuline G1 humaine-(229 résidus C-terminaux)-peptide (fragment Fc)]  
immunomodulateur

riloncept  
(659-659':662-662')-bisdisulfuro del dímero de la 
[653-glicina]proteína accesoria del receptor de la interleukina-1 humana-(1-339)-péptido (fragmento del dominio extracelular) proteína de fusión con el receptor de tipo I humano de la interleukina-1-(5-316)-péptido (fragmento del dominio extracelular) proteína de fusión con la inmunoglobulina G1 humana-(229 restos C-terminales)-péptido (fragmento Fc)]  
inmunomodulador

C_{15}H_{10}FNO_{3}  
524684-52-4

Monomer / Monomère / Monómero

SERCDDWGLD TMRQIQVFED EPARIKCPLF EHFLKFNSTY AHSAGLTLIW 50
YWTRQDRDLE EPINFRLPEN RISKEKXVVKL FRPTLDNCTG HYTCMLHNIT 100
YCAVAPFPLE VQGPSCSTPN HWKLPMHNLX IEYGIQDTCX RINQGQFTES 150
VPKFTYWPH CYRLOQFRNY IDEGMLWSFL IALISNHGRY TVCVCYRPHG 200
RTPQILYTLT VYVKEGSMYP VPVSWVSPFD RYVTKYEPQG ELLIPCTYVF 250
SRFGDQETPH WRTIDCNGPG D171QYFISE EISBHRTEDE YPPKLTTSLK 300
VTSCDRLKGY VCRAABKAEG VAKAXXVQKR VPAPYPTVEK CKRKEKXILL 350
VSAIARRRVR PCPCPEXORX GTITWOXGDX KTPQPOQXAS RHNQKXKXNL 400
FVPKAVYEGG YHCYQVision YCLRXXSAX PXVLQDNCX QAATPQFKRL 450
PVAQDDLGLYC FYREFFXKXK RNYLFQKWYX OCRPPLLHSG HSFQKDRKLI 500
VMNVASKFHLG HYTCMASFY GCTPQFQMQX IEPVALXEBK RYPVPVQSA 550
NETMVELOG QIPLIQCMQTC QLSLIAVWNY MSSVIEDDDP VLQQDYPSVL 600
HPPWREGAIL YVDAISDKH SRFFARPFCT PAHKWVIDGA AYVLIPYPV 650
NSCQKTNCPT PCAPALLLGC PGLVLFPFPG CDLMIRKSTP EVTCVVMQV 700
HEDIPRTYKYN VDGQVYVWKA KTFRKPEQYN STPVYTVSTV TLVQWNLAXK 750
YRCKVSNKA LPAIREKTI5 KAKGGQFPEQ VTLYPPSGOE LTRQQVSLTC 800
LVEQGQFGSI ANEWSNQGPQ ENNYTPFPVS LDGDFCSFLY SKLTVOKSHV 850
QQQVYVFSGCV NHEALNMYRT QKXHLSGPK 900

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

C_{90}H_{139}N_{24}O_{26}S_{7}  
501081-76-1
rosabulinum
rosabulin
2-{3-[(4-cyanophenyl)methyl]indolizin-1-yl]-N-(3-methyl-1,2-thiazol-5-yl)-2-oxoacetamide
antineoplastic

rosabuline
2-[3-[(4-cyanobenzyl)indolizin-1-yl]-N-(3-méthylisothiazol-5-yl)-2-oxoacétamide
antinéoplasique

rosabulina
2-[3-[(4-cianobencil)indolizin-1-il]-N-(3-metilisotiazol-5-il)-2-oxoacetamida
antineoplásico

C_{22}H_{16}N_{4}O_{2}S
501948-05-6

sagopilonum
sagopilone
(1S,3S,7S,10R,11S,12S,16R)-7,11-dihydroxy-8,8,12,16-tetramethyl-3-(2-methyl-1,3-benzothiazol-5-yl)-10-[(prop-2-enyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
antineoplastic

sagopilone
(-)-(1S,3S,7S,10R,11S,12S,16R)-7,11-dihydroxy-8,8,12,16-tétraméthyl-3-(2-méthyl-1,3-benzothiazol-5-yl)-10-[(prop-2-ényl)-4,17-dioxabicyclo[14.1.0]heptadécane-5,9-dione
antinéoplasique

sagopilona
(1S,3S,7S,10R,11S,12S,16R)-7,11-dihidroxi-8,8,12,16-tetrametil-3-(2-metil-1,3-benzotiazol-5-il)-10-[(prop-2-enil)-4,17-dioxabiciclo= [14.1.0]heptadecano-5,9-diona
antineoplásico

C_{30}H_{41}NO_{6}S
305841-29-6
sodelglitazarum
sodelglitazar
2-{4-[[2-fluoro-4-(trifluoromethyl)phenyl]-4-methyl-1,3-thiazol-5-yl]-methyl}sulfanyl]-2-methylphenoxy]-2-methylpropanoic acid
antidiabetic

sodelglitazar
acide 2-{4-[[2-fluoro-4-(trifluorométhyl)phényl]-4-méthyl-1,3-thiazol-5-yl][méthyl][sulfanyl]-2-méthylphénoxy]-2-méthylpropanoïque
antidiabétique

sodelglitazar
ácido 2-{4-[[2-fluoro-4-(trifluorometil)fenil]-4-metil-1,3-tiazol-5-il][metil]= sulfanil]-2-metifenoxi]-2-metilpropanoico
hipoglucemiante

C_{23}H_{21}F_4NO_3S_2  447406-78-2

sologatranum
sologatran
propyl [(1S)-1-[(2S)-2-[[trans-4-aminocyclohexylmethyl]carbamoyl]-pyrrolidine-1-carbonyl]-2-methyl-2-[[propan-2-yl]sulfanyl]propyl]= carbamate
thrombin inhibitor

sologatran
[(1S)-1-[(2S)-2-[[trans-4-aminocyclohexylméthyl]carbamoyl]-pyrrolidin-1-y]-carbonyl]-2-méthyl-2-[[1-méthyléthyl]sulfanyl]propyl]= carbamate de propyle
inhibiteur de la thrombine

sologatrán
inhibidor de la trombina

C_{24}H_{44}N_4O_4S  187602-11-5

sucinobucolum
succinobucol
4-[[2-[[3,5-di-tert-butyl-4-hydroxyphenyl]sulfanyl]propan-2-yl]= sulfanyl]-2,6-di-tert-butlyphenoxy]-4-oxobutanoic acid
anti-inflammatory
sucinobucol  acide 4-[[1-[3,5-bis(1,1-diméthyléthyl)-4-hydroxyphényl]sulfanyl]-1-méthyléthyl]sulfanyl]-2,6-bis(1,1-diméthyléthyl)phényl]-4-oxobutanoïque  anti-inflammatoire

sucinobucol  ácido 4-[[2-[3,5-di-terc-butil-4-hidroxifenil]sulfanil]propan-2-il]sulfanil]-2,6-di-terc-butifenoxi]-4-oxobutanoico  antiinflamatorio

\[
C_{36}H_{52}O_5S_2 \quad 216167-82-7
\]

**taribavirinum**

**taribavirin**  1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboximidamide  antiviral

**taribavirine**  1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboximidamide  antiviral

**taribavirina**  1-β-D-ribofuranosil-1H-1,2,4-triazol-3-carboximidamida  antiviral

\[
C_{9}H_{13}N_5O_4 \quad 119567-79-2
\]

tezampanelum  tezampanel  (3S,4aR,6R,8aR)-6-[2-(1H-tétrazol-5-il)éthyl]=décahydrossoquilinéine-3-carboxylique  antagoniste des récepteurs AMPA/KA du glutamate

**tézampanel**  (−)-acido (3S,4aR,6R,8aR)-6-[2-(1H-tetrazol-5-il)etil]=decahidroisoquinolina-3-carboxílico  antagonista de los receptores AMPA/KA de glutamato

\[
C_{13}H_{21}N_5O_2 \quad 154652-83-2
\]
ticagrelorum
ticagrelor
\[(1S,2S,3R,5S)-3-(7-[(1R,2S)-2-(3,4-difluoropheny]cyclopropyl)\)amino]-5-(propylsulfanyl)-3H\{-1,2,3\}triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol
platelet aggregation inhibitor

ticagrélor
ticagrelor
\[(1S,2S,3R,5S)-3-(7-[(1R,2S)-2-(3,4-difluorophényl)cyclopropyl)]\)amino]-5-(propylsulfanyl)-3H\{-1,2,3\}triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol
antiagrégant plaquettaire

C\textsubscript{23}H\textsubscript{28}F\textsubscript{2}N\textsubscript{6}O\textsubscript{4}S
274693-27-5

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tigapotidum
tigapotide
antineoplastic

tigapotide
antinéoplasique

tigapotida
\[S^{37},S^{38},S^{42}\]-tris[acetilamino]metil]beta-microseminoproteína humana (proteína PSP94 secretada por la próstata)-(31-45)-péptido
antineoplásico

C\textsubscript{82}H\textsubscript{119}N\textsubscript{21}O\textsubscript{34}S\textsubscript{3}
848084-83-3

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tipelukastum
tipelukast
4-(6-acetyl-3-[3-[4-acetyl-3-hydroxy-2-propylphenyl)sulfonyl]=propoxy)-2-proplyphenoxylbutanoic acid
leukotriène receptor antagonist

---
tiptelukast  
acide \(4\text{-}[6\text{-acétyl-3-[3\text{-}[4\text{-acétyl-3-hydroxy-2-propylphényl]}\text{sulfanyl=propoxy-2-propylphénoxy]}\text{butanoïque}}\)

antagoniste du récepteur des leucotriènes

tiptelukast  
ácido \(4\text{-}[6\text{-acetil-3-[3\text{-}[4\text{-acetil-3-hidroxi-2-propilfenil]}\text{sulfanil=propoxi-2-propilfenoxi]}\text{butanoico}}\)

antagonista del receptor de leucotrienos

C_{29}H_{38}O_{7}S  
125961-82-2

tomopenenem  
\((4R,5S,6S)-3-\text{[[(3S,5S)-5-[(3S)-3-(carbamimidadidoacetamido)=pyrrolidine-1-carbonyl]-1-methylpyrrolidin-3-y]sulfanyl]-6-\text{[1R]-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid}}\)
antibiotic

tomopenem  
ácido \((4R,5S,6S)-3-\text{[[(3S,5S)-5-[(3S)-3-(carbamimidamidoacetamido)=pyrrolidin-1-carbonyl]-1-methylpyrrolidin-3-y]sulfanyl]-6-\text{[1R]-1-hidroxietil]-4-metil-7-oxo-1-zabiciclo[3.2.0]hept-2-eno-2-carboxilico}}\)
antibiotico

tylvalosinum  
\((4R,5S,6S,7R,9R,11E,13E,15R,16R)-15-\text{[(6-deoxy-2,3-di-O-methyl-β-o-allopyranosyl)oxy)methyl]-6-\text{[3,6-dideoxy-4-O-[2,6-dideoxy-3-C-methyl-4-O-(3-methylbutanoyl)-\text{o-L-ribo-hexopyranosyl]-3-(dimethylamino)-β-glucopyranosyl]oxy]-16-ethyl-5,9,13-trimethyl-2,10-dioxo-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-4-yl acetate}}\)
antibiotic
tylvalosine


C_{53}H_{87}NO_{19} 63409-12-1

vabicaserinum

vabicaserin

(9a\,R^*,\,12a\,S^*)-4,5,6,7,9,9a,10,11,12,12a-decahydrocyclopenta[c][1,4]diazepino[6,7,1-ij]quinoline serotonin receptors agonist, antipsychotic

C_{15}H_{20}N_{2} 620948-93-8

vapitadinum

vapitadine

5,6-dihydrospiro[imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-carboxamide tricyclic histamine H_{3} receptor antagonist
vapitadine  
5,6-dihydrospiro[11H-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-carboxamide  
antagoniste tricyclique du récepteur H1 de l'histamine

vapitadina  
5,6-dihidrospiro[11H-imidazo[2,1-b][3]benzazepina-11,4'-piperidina]-3-carboxamida  
antagonista tricíclico del receptor H1 de histamina

C_{17}H_{20}N_{4}O  
793655-64-8

veliflaponum  
veliflapon  
(2R)-cyclopentyl[4-[(quinolin-2-yl)methoxy]phenyl]acetic acid  
5-lipoxygenase activating protein (FLAP) antagonist

vélfalpon  
(+)-acide (2R)-cyclopentyl[4-(quinoléin-2-ylméthoxy)phényl]acétique  
inhibiteur de la protéine activant la 5-lipoxygenase (FLAP)

veliflapón  
(+)-ácido (2R)-ciclopentil[4-(quinolin-2-ilmetoxi)fenil]acético  
antagonista de la proteína activadora de la 5-lipoxigenasa (FLAP)

C_{23}H_{23}NO_{3}  
128253-31-6

volinanserinum  
volinanserin  
(R)-(2,3-dimethoxyphenyl)[1-2-(4-fluorophenyl)ethyl]piperidin-4-yl)methanol  
serotonin receptor antagonist

volinansérine  
(+)-(R)-(2,3-diméthoxyphényl)[1-2-(4-fluorophénoxy)éthyl]pipéridin-4-il)méthanol  
antagoniste des récepteurs de la sérotonine

volinanserina  
(+)-(R)-(2,3-dimetrofenil)[1-2-(4-fluorofenil)etil]pipéridin-4-il]metanol  
antagonista del receptor de la serotonina

C_{22}H_{28}FNO_{3}  
139290-65-6
AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Proposed International Non Proprietary Names (Prop. INN): List 44
Dénominations communes internationales proposées (DCI Prop.): Liste 44
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 44
(WHO Chronicle, Vol. 34, No. 9, 1980)

p. 26 delete/supprimer/suprímase insert/insérer/insertése
docusatum natricum natrii docusas

Proposed International Non Proprietary Names (Prop. INN): List 87
Dénominations communes internationales proposées (DCI Prop.): Liste 87
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 87

p. 180 pegsunercept pegsunercept pegsunercept tumor necrosis factor antagonist tumor necrosis factor antagonist pegsunercept pegsunercept pegsunercept pegsunercept pegsunercept pegsunercept pegsunercept pegsunercept pegsunercept pegsunercept pegsunercept pegsunercept

Proposed International Non Proprietary Names (Prop. INN): List 91
Dénominations communes internationales proposées (DCI Prop.): Liste 91
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 91

p. 167 delete/supprimer/suprímase insert/insérer/insertése
gantacurium chloridum gantacurii chloridum
gantacurium chloridum gantacurii chloridum

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gantacurium chloridum gantacurii chloridum

Proposed International Non Proprietary Names (Prop. INN): List 92
Dénominations communes internationales proposées (DCI Prop.): Liste 92
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 92
(WHO Drug Information, Vol. 18, No. 4, 2004)

p. 325 delete/supprimer/suprímase insert/insérer/insertése
artemifonum artemisonum
artemifone artemisone
artémifone artémisone
artemifona artemisona

p. 335 suprímase insertése
epoetina zeta epoetina dseta
Proposed International Non Proprietary Names (Prop. INN): List 94
Dénominations communes internationales proposées (DCI Prop.): Liste 94
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 94
(WHO Drug Information, Vol. 19, No. 4, 2005)

p. 316  
**alcaftadimum**  
alcaftadine  
alcaftadina  
replace the chemical name by the following:  
sustitúyase el nombre químico por el siguiente:  
11-[(1-methylpiperidin-4-ylidene)-6,11-dihydro-5H-imidazo[2,1-b][3]benzazepine-3-carbaldehído  
11-[(1-metilpiperidin-4-ilideno)-6,11-dihidro-5H-imidazo[2,1-b][3]benzazepina-3-carbaldehido

p. 321  
**celivaronum**  
celivarona  
sustitúyase el nombre químico por el siguiente:  
2-butil-3-[4-[3-(dibutilamino)propil]benzoil]-1-benzofurano-5-carboxilato de isopropilo

p. 321  
**cevoglitazarum**  
cevoglitazar  
replace the chemical name by the following:  
sustitúyase el nombre químico por el siguiente:  
(2R)-1-[4-[5-metil-2-[4-(trifluorometil)fenil]oxazol-4-il]metiloxo]-1H-indole-2-carboxylic acid

p. 323  
**denagliptinum**  
denagliptina  
sustitúyase el nombre químico por el siguiente:  
(2S,2S)-2-aminod-3,3-bis(4-fluorofenil)propanoil-4-fluoropirrolidina-2-carboxitrilo

p. 331  
**lisdexanfetaminum**  
lisdexanfetamina  
sustitúyase el nombre químico por el siguiente:  
(2S)-2,6-diamino-N-[(1S)-2-fenil-1-metiletil]hexanamida

p. 331  
**lodenañil carbonas**  
carbonato de lodenañilo  
sustitúyase el nombre químico por el siguiente:  
carbonato de bis(2-[4-[4-etoxi-3-(1-metil-7-oxo-3-propil-4,7-dihidro-1H-pirazolo[4,3-d]pirimidin-5-il]fenilsulfonil)piperazin-1-il]etil)

p. 332  
**masilukastum**  
masilukast  
sustitúyase el nombre químico por el siguiente:  
1-metil-3-[(2-[4-(metilfénil)sulfonil]carbamoil)fenil]metil-2-metoxi-1H-pirimidin-5-ilamida

p. 333  
**nilotinibum**  
nilotinib  
sustitúyase el nombre químico por el siguiente:  
4-metil-N-[3-(4-metil-1H-imidazol-1-il)-5-(trifluorometil)fenil]-3-[4-(pirimidin-3-il)amino]benzamida

p. 334  
**ocrelizumabum**  
ocrelizumab  
replace the molecular formula by the following:  
remplacer la formule brute par la suivante:  
sustitúyase la fórmula molecular por la siguiente:  
C_{6494}H_{9298}N_{1718}O_{2014}S_{46}
parogrelilum
 replace the action and use by the following:
inhibition of PDE-III, PDE-V and TxA<sub>2</sub> synthetase

relacatibum
 replace the chemical name by the following:
N-{[(1S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-[(piridin-2-ylsulfonyl)hexahydro-1H-azeopin-4-yl]carbamoyl]butyl]-1-benzofuran-2-carboxamide

stamulumabum
 replace the definition by the following:
immunoglobuline G1, anti-(facteur 8 de croissance/différenciation (GDF-8 ou myostatine) humain) ; dimère du disulfure entre la chaîne lourde et la chaîne λ de l’anticorps monoclonal humain MYO-929

ticilimumabum
 replace the molecular formula by the following:
C<sub>6500</sub>H<sub>9974</sub>N<sub>1726</sub>O<sub>2026</sub>S<sub>52</sub>

tramiprosatum
 replace the action and use by the following:
inhibition of amyloid β fibril formation and deposition

transferrinum aldifitoxum
 replace the molecular formula by the following:
C<sub>5992</sub>H<sub>9317</sub>N<sub>1641</sub>O<sub>1834</sub>S<sub>63</sub>

tucotuzumabum celmoleukinum
 replace the molecular formula by the following:
C<sub>7812</sub>H<sub>12114</sub>N<sub>2042</sub>O<sub>2406</sub>S<sub>60</sub>

supprimer insérer vélafermin vélafermine
p. 349  **verpasepum caltespenuem**  
verpasep caltespeno  
*sustitúyase la descripción por la siguiente:*  
60 kDa chaperonina 2 (HSP 65 de *Mycobacterium bovis* cepa BCG) proteína de fusión con la L-histidilproteína E7 del papilomavirus humano 16

p. 350  **zibotentanum**  
zibotentán  
*sustitúyase el nombre químico por el siguiente:*  
N-(3-metoxi-5-metilpirazin-2-il)-2-[4-(1,3,4-oxadiazol-2-il)fenil]piridina-3-sulfonamida

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

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 Organization1 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.1

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.1

   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.

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

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

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

9. Group relationship in INN (see 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. Where a stem is shown without any hyphens it may be used anywhere in the name.

<table>
<thead>
<tr>
<th>Latin</th>
<th>English</th>
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<td>-acum</td>
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1 A more extensive listing of stems is contained in the working document WHO/EDM/QSM 2004.5 which is regularly updated and can be requested from the INN Programme, WHO, Geneva.
Annexe 1

PROCEDURE A SUIVRE EN VUE DU CHOIX DE DENOMINATIONS COMMUNES INTERNATIONALES RECOMMANDEES POUR LES SUBSTANCES 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 États Membres et aux commissions nationales de pharmacopée ou autres organismes désignés par les États 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 États Membres de prendre les mesures nécessaires pour prévenir l’acquisition de droits de propriété sur la dénomination proposée pendant la période au cours de laquelle cette dénomination est mise à l’étude par l’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).

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’aucune des objections formulées, 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 États 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 États 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 appellations déjà couramment employées.

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

* 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.

1 Depuis janvier 1959, cette publication porte le titre de Chronique OMS. À partir de 1987, les listes des DCI sont publiées dans les Informations pharmaceutiques OMS.
Outre ces deux principes fondamentaux, on respectera les principes secondaires suivants:

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

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

5. Les DCI pour les substances utilisées sous forme de sels devront en général s’appliquer à la base active (ou à l’acide actif). Les dénominations pour différents sels ou esters d’une même substance active ne différeront que par le nom de l’acide inactif (ou de la base inactive).

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

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

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

8. On tiendra compte 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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substances anti-inflammatoires dérivées de l’ibufénac
annotésiques
anti-asthmatiques, anti-allergiques n’agissant pas principalement en tant qu’antihistaminiques
antihistaminiques
substances dérivées du diazépam
stéroïdes anabolisants
antiarhythmiques de classe I, dérivés de la procainamide et de la lidocaine
anesthésiques locaux
antibiotiques dérivés de l’acide céphalosporanique
antibiotiques dérivés de l’acide amino-6 pénicillanique
agents antifongiques systémiques dérivés du miconazole
corticostéroïdes autres que les dérivés de la prednisolone
inhibiteurs sélectifs de la cyclo-oxygénase
antagonistes du récepteur de l’endothéline
agents gabamimétiques
produits à usage diagnostique dérivés du gadolinium
antithrombotiques
stéroïdes progestogènes
agents antihyperglycémiants
produits de contraste iodés

1 Une liste plus complète de segments clés est contenue dans le document de travail WHO/EDM/QSM 2004.5 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\(^1\) 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.


\(^{1}\) 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. Cada 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. Cada 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.
1. Las Denominaciones Comunes Internacionales (DCI) deberán diferenciarse tanto fonéticamente como ortográficamente. No deberán ser incómodamente largas, ni dar lugar a confusión con denominaciones de uso común.

2. La DCI de una sustancia que pertenezca a un grupo de sustancias farmacológicamente emparentadas deberá mostrar apropiadamente este parentesco. Deberán evitarse 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.

1 El documento de trabajo WHO/EDM/GSM 2004.5, que se pone al día regularmente, contiene una lista más extensa de partículas comunes. Las personas que deseen recibirlo deberán solicitar su envío al Programa DCI, OMS, Ginebra (Suiza).
### Latin | Español
--- | ---
-acum | -aco  | antiinflamatorios derivados del ibufenaco
-adolum | -adol  | analgésicos
-adol- | -adol- | 
-astum | -ast  | antiasmáticos, sustancias antialérgicas cuya acción principal no es la antihistamínica
-astinum | -astina  | antihistamínicos
-azejamum | -azejam  | derivados del diazemum
bol | bol  | esteroides anabolizantes
-caín- | -caína-  | antiarrítmicos de clase I, derivados de procainamida y lidocaína
-caínunum | -caína-  | anestésicos locales
-cef- | cef-  | antibióticos, derivados del ácido cefalosporánico
-célinum | -cilina  | antibióticos derivados del ácido 6-aminopenicilánico
-conazolum | -conazol  | antifúngicos sistémicos derivados del miconazol
-cort | cort  | corticosteroides, excepto derivados de prednisolona
-coxibum | -coxib  | inhibidores selectivos de ciclooxigenasa
-entanum | -entán  | antagonistas del receptor de endotelina
-gab | gab  | gabamiméticos
-gado- | gado-  | agentes para diagnóstico derivados de gadolinio
-gartranum | -gartrán  | inhibidores de la trombina antitrombóticos
-gest | gest  | esteroides progestágenos
-gli | gli  | hipoglucemiantes, antihiperglúcémicos
-io- | io-  | medios de contraste iodados
-metacinum | -metacina  | antiinflamatorios derivados de indometacina
-mycinum | -micina  | antibióticos producidos por cepas de *Streptomyces*
-nidazolum | -nidazol  | antiprotozoarios derivados de metronidazol
-ololum | -olol  | antagonistas de receptores β-adrenérgicos
-oxacinum | -oxacino  | antibacterianos derivados del ácido nalidíxico
-platinum | -platino  | antineoplásicos derivados del platino
-poetinum | -poetina  | factores sanguíneos similares a la eritropoyetina
-pril(at)um | -pril(at)  | inhibidores de la enzima conversora de la angiotensina
-profenum | -profeno  | antiinflamatorios derivados del ibuprofeno
-prost | prost  | prostaglandinás
-relinum | -reлина  | péptidos estimulantes de la liberación de hormonas hipofisarias
-sartanum | -sartán  | antihipertensivos (no peptídicos) antagonistas del receptor de angiotensina II
-vaptanum | -vaptán  | antagonistas del receptor de vasopresina
-vin- | vin-  | alcaloides de la vinca
-vin- | vin-  | )