RECOMMENDED INN LIST 46
INTERNATIONAL NONPROPRIETARY NAMES
FOR PHARMACEUTICAL SUBSTANCES

WORLD HEALTH ORGANIZATION • GENEVA
WHO Drug Information

is now available at:

http://www.who.int/druginformation
Internet pharmacies: advantages and risks

Harri Ovaskainen
Director for Pharmaceutical Affairs
Finnish Pharmacists Association
Helsinki, Finland

The Internet, first developed as a resource to facilitate communication, has now grown into a global network of computer systems that link multiple platforms and create interrelationships between governments, academic institutions, businesses and consumers. Although experts predict that over 380 million people will be online by 2003, approximately 88% of all Internet users are presently situated in industrialized countries (1).

Within this global perspective, industry analysts have projected that Internet pharmacies will generate US$ 1.4 billion in prescription drug sales by 2001 and over US$ 15 billion by 2004. Currently, over 400 businesses dispensing prescription drugs operate on the Internet. Many of these websites, however, deliver prescription drugs without a valid prescription, dispense drugs of questionable quality, and fail to provide adequate independent information to patients on possible adverse reactions and drug interactions. Additionally, customers have difficulty knowing whether an Internet pharmacy is a legitimate operation (2).

In 1997, the World Health Organization called on its Member States to tighten controls on the sale of medical products through the Internet. WHO was especially concerned that Internet sales may bypass national drug regulatory authorities, thereby liberating medical products onto the market which are unapproved, fraudulent, unsafe, or ineffective. WHO has declared that ordering medical products without the safeguards offered by competent regulation could endanger public health and pose a risk to individual patients (3).

Possible risks of e-commerce pharmaceuticals

Under present conditions, patients can obtain prescription medications over the Internet in several ways. First, in some countries they can request direct delivery of medications if their doctor submits a prescription by telephone or a script attachment. Alternatively, patients can contact their physician over the Internet, request a medication, and have the physician transmit the prescription to the online pharmacy. Compared to the first model, this approach allows the patient’s pharmacist to review the prescription although it bypasses a visit to the physician. Thirdly, consumers can order medications directly over the Internet without seeing a physician or a pharmacist. The latter method is associated with the greatest potential risk to the consumer because it does not require a visit to the physician or review by a pharmacist (4).

The danger for consumers of purchasing medicines in this way cannot be underscored, since they will not be provided with sufficient information allowing them to distinguish between legal on-line pharmacies and illegal commercial sites selling any kind of medical products. To gain consumer confidence and make a clearer distinction between legal and illegal sites, the United States National Association of Boards of Pharmacy (NABP) has developed the Verified Internet Pharmacy Practice Sites (VIPPS) programme (5). To be VIPPS certified, a pharmacy must comply with the licensing and inspection requirements of their State and each State to which they dispense pharmaceuticals. If the pharmacy has demonstrated to NABP compliance with VIPPS criteria, it will display the VIPPS hyperlink seal on its website. VIPPS criteria include patient rights to privacy, authentication and security of prescription orders, adherence to a recognized quality assurance policy, and provision of meaningful consultation between patients and pharmacists.

On the other hand, if a patient buys medicines from an illegal commercial site there is a total absence of any quality guarantee covering the medicine. This means that medicines may be counterfeit or substandard or even unapproved new drugs. Illegal websites selling pharmaceuticals do not have counselling services by health-care professionals and they have been identified as selling prescription-only drugs such as antibiotics, toxic chemotherapy regimens or anti-acne drugs that can cause birth defects. These sites also have misleading advertising and information: products are offered as suitable for self-care which, when used in the wrong
way, may have serious consequences. Other products are presented as medicines which may not have any proven therapeutic effect.

Some Internet pharmacies offer online prescribing only upon completion of a short questionnaire by the purchaser. Typically, it is claimed that the questionnaire is reviewed by a doctor and the drug is only prescribed if the doctor approves the questionnaire (6), however, this is difficult to verify. To address this concern, the American Medical Association has declared that any health care practitioner who offers a prescription to a patient solely on the basis of an on-line questionnaire without having ever examined the patient has not met the appropriate medical standard of care (7).

Different organizations have warned consumers not to purchase medicines via the Internet. WHO has published a document “Medical products and the Internet: A guide to finding reliable information” (8). National authorities such as the US Food and Drug Administration (FDA) has published tips and warnings for consumers in the Internet to make people aware of the dangers of buying medical products online (9). Professional pharmaceutical and medical bodies such as the Pharmaceutical Group of the European Union (PGEU) and Standing Committee of European Doctors (CP) have released their own document “The Internet and Medicines: enjoy the Internet but don’t risk your health!” (10). Other related risks are a lack of security for payments, possible disclosure of confidential information, or mishandling of personal data. In Internet transactions, the supplier is processing confidential personal data which includes information on the physical and mental health of individuals.

While ordering routines can technically be handled via the Internet, the issue of physical delivery remains. There are two concerns. One is that delivery does not take place immediately — online pharmacies must also invest in delivery points to be able to guarantee delivery on time. The second concern is safety of delivery whereby packages are sent to homes by mail or by express delivery without the certainty that the customer is actually there and without being able to control exactly what happens to the package at delivery (11). Regular mail delivery does not ensure that packages of pharmaceuticals will arrive undamaged, and in some countries either hot or extremely cold weather may cause changes to the product.

The benefits of e-commerce pharmaceuticals

The greatest benefit for many individuals in obtaining medicines through the Internet is simplicity and convenience. However, it is also easy for a customer to access illegal drug selling sites and order a product simply by providing a credit card number. International regulations require drugs to be declared at the post office to which they are sent, but companies may dispatch packages unmarked.

Legitimate Internet pharmacies usually require patients to register and will offer services such as consultation with a pharmacist by telephone or e-mail. When working well, the legitimate online pharmacies also try to avoid potential drug interactions by asking new patients to complete a form indicating what other medications they are currently taking, giving a medical history, and describing related health conditions. Each patient is provided with a unique personal identifier and confidential patient-specific information is only transmitted following entry of this number. The patient is sometimes offered the opportunity to participate (“opt-in”) in various programmes which the pharmacy offers such as e-mail prescription refill reminders (12).

The Internet offers convenience and privacy for persons buying on-line while providing expanded access to prescription drugs and health care practitioners. Through the Internet, the disabled, the elderly, and patients living in remote areas can easily obtain information, products and services that were previously acquired only with great difficulty. Also, price differences are quite often important. Internet pharmacies are generally 10% lower in the USA despite transportation charges (13).

The challenge for pharmacy regulators is now to develop a regulatory approach that will prevent the dangers described, while leaving unaffected the online innovations that can enhance the appropriate use of medications and improve a patient’s quality of life. A report on the outcomes of several surveys, including an analysis of responses provided by drug regulatory authorities to a WHO questionnaire can be found on page 181.

References


5. Verified Internet Pharmacy Practice Sites (VIPPS™). A Program of the National Association of Boards of Pharmacy. [http://vipps.nabp.net/verify.asp](http://vipps.nabp.net/verify.asp)


Reports on Individual Drugs

Atypical antipsychotics and impaired glucose metabolism

Jenna Griffiths and Pascale Springuel, Bureau of Licensed Product Assessment, Therapeutic Products Directorate, Health Canada*

The new atypical antipsychotics clozapine, olanzapine, quetiapine and risperidone are among first-line treatments for managing psychotic disorders mainly because they are associated with superior effectiveness in controlling the negative symptoms of schizophrenia — blunted affect, emotional and social withdrawal (1).

Some atypical antipsychotics have been associated with impaired glucose metabolism (2). Since 1994, there have been at least 29 published cases of impaired glucose metabolism associated with the use of clozapine and 26 with olanzapine (2, 3) and since February 1999, there have been two published cases in which risperidone was associated with diabetic ketoacidosis or elevated blood glucose levels (4, 5) and two published cases of new-onset diabetes mellitus with quetiapine (2, 6).

In 1999, the results of a cross-sectional study revealed a possible association between type 2 diabetes and antipsychotics (7). Specifically, diabetes was diagnosed in 15.5% of schizophrenic patients treated with clozapine, 11% of those treated with olanzapine and 6% of those treated with risperidone (7). Clozapine, olanzapine, quetiapine and risperidone were introduced in Canada in 1991, 1996, 1997 and 1993 respectively. By June 2001, a total of 37 domestic case reports of suspected impaired glucose metabolism associated with these drugs were reported to the Canadian Adverse Drug Reaction Monitoring Program. Patient characteristics and important adverse reactions are summarized in Tables 1 and 2 overleaf, respectively.

In 17 of the 37 cases, the reactions occurred within five months of treatment onset. Similarly, in published cases, impaired glucose metabolism associated with atypical antipsychotics often occurred relatively soon following the start of treatment, i.e. in as little as 10 days with clozapine, 15 days with olanzapine and one month with quetiapine (2). Of the 35 reports in which disorders of hyperglycaemia were denoted, there were four cases of pre-existing diabetes; 24 cases were considered to be new onset on the basis of the evidence in the report, with 14 clearly noted as being new-onset diabetes mellitus. One of the cases occurred 2 weeks after discontinuation of risperidone therapy and involved an intentional overdose. There were two reports of hypoglycemia; both patients had a prior history of diabetes before this reaction.

Of the 10 cases in which “diabetic ketoacidosis” or “ketoacidosis” was reported (Table 2), the possibility of alcohol consumption or substance use was noted in four cases, and abnormal liver function test results were reported in two cases. Three of these 10 patients died. Schizophrenic patients may be predisposed to diabetes mellitus and associated disorders due to factors such as reduced physical activity, poor diet and co-existing illnesses (8). In addition, the involvement of concomitant medications such as divalproex sodium, (9,10) lithium, (10) and other drugs metabolized by the liver (11, 12) cannot be ruled out as contributing to the abnormal glucose metabolism associated with clozapine (12, 13) or olanzapine (10, 11). Other risk factors for hyperglycemia or ketoacidosis in patients taking clozapine or olanzapine may include being male, non-White and age of about 40 years (14).

Obesity is another major risk factor for diabetes(14). Among the Canadian reports, there was one case of a 33-year-old man who took olanzapine (15 mg/day) and gained between 22 and 45 kg over 1 year after starting olanzapine therapy. It was reported that diabetes developed as a result of this weight gain. It has been speculated that multiple receptor antagonism (dopamine, serotonin, histamine) may be involved in the development of non-insulin-dependent diabetes mellitus associated with atypical antipsychotics (2). Specifically, antagonism of histaminic and possibly serotonergic receptors may induce weight gain, which in turn, may lead to...

* Full text appears in Canadian Adverse Drug Reaction Newsletter, Volume 11, Number 4, October 2001.
### Table 1: Characteristics of patients with impaired glucose metabolism associated with atypical antipsychotics reported to the Canadian Adverse Drug Reaction Monitoring Program as of June 7, 2001

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 17&lt;sup&gt;2&lt;/sup&gt;</td>
<td>n = 10&lt;sup&gt;3&lt;/sup&gt;</td>
<td>n = 3&lt;sup&gt;4&lt;/sup&gt;</td>
<td>n = 7&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Mean age (and range), yr</td>
<td>45 (26–74)</td>
<td>34 (26–46)</td>
<td>30 (30)</td>
<td>48 (11–78)</td>
</tr>
<tr>
<td>Female : male ratio</td>
<td>6:10&lt;sup&gt;6&lt;/sup&gt;</td>
<td>4:6</td>
<td>0:2&lt;sup&gt;6&lt;/sup&gt;</td>
<td>6:1</td>
</tr>
<tr>
<td>Period of onset of impaired glucose metabolism</td>
<td>18 d to 6.5 yr</td>
<td>11 d to 5 yr</td>
<td>2.5 to 4 mo</td>
<td>2 d to 8 mo&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Daily dose of atypical antipsychotic</td>
<td>100 to 775 mg</td>
<td>7.5 to 30 mg</td>
<td>300 to 700 mg</td>
<td>1 to 6 mg&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Maximum recommended daily dose</td>
<td>900 mg</td>
<td>20 mg</td>
<td>750 mg</td>
<td>6 mg</td>
</tr>
</tbody>
</table>

<sup>1</sup>These data cannot be used to determine the incidence of ADRs because neither the prescribing rate nor the amount of time the drug was on the market has been taken into consideration.

<sup>2</sup>Concomitant medication was risperidone (6 mg/d) in 1 case.

<sup>3</sup>Clozapine and olanzapine were reported as co-suspect medications in 1 case report, but from the evidence provided, olanzapine was considered the suspect drug.

<sup>4</sup>Quetiapine and risperidone were reported as co-suspect medications in 1 case report, but from the evidence provided, quetiapine was considered the suspect drug.

<sup>5</sup>Age not specified in 1 case.

<sup>6</sup>Sex not specified in 1 case.

<sup>7</sup>Case of overdose not included.

### Table 2: Glucose-related reaction terms reported in the Canadian case reports associated with clozapine, olanzapine, quetiapine, risperidone

<table>
<thead>
<tr>
<th>Reaction term</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma diabetic</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diabetic ketoacidosis/ketoacidosis&lt;sup&gt;2&lt;/sup&gt;</td>
<td>5&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>4</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Labile blood sugar&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>1</sup>Based on the “preferred term” of the World Health Organization (WHO) Adverse Reaction Dictionary (WHOART). Each report may contain more than 1 of these reaction terms, however, reports were only included in the most significant category.

<sup>2</sup>Terminology other than WHO “preferred term” was used.

<sup>3</sup>One case also involved “coma diabetic.”
changes in glucose metabolism, and that these changes may have a causal role in neuroleptic-induced hyperglycemia (11). Serotonin antagonism may decrease the responsiveness of pancreatic cells, which would result in low insulin levels and ensuing hyperglycemia (11). Diabetes induced by atypical antipsychotics may be attributed to multiple factors, and the mechanism of action remains unclear (2). Atypical antipsychotics may be associated with new-onset diabetes mellitus and diabetic ketoacidosis. Patients may require glucose monitoring upon initiation and titration of antipsychotic medications, and regular monitoring thereafter (15, 16).

References


Antituberculosis drugs: hepatobiliary reactions

Duc Vu and Lynn Macdonald, Bureau of Licensed Product Assessment, Therapeutic Products Directorate, Health Canada

According to the latest edition of the Canadian Tuberculosis Standards (1) Canada has one of the lowest reported incidence rates of tuberculosis (TB) in the world. However, in Canada, the high-risk groups for Mycobacterium tuberculosis infection are HIV-positive people, Aboriginals, foreign-born people from countries with a high prevalence of TB, intravenous drug users and homeless people.

The Canadian Lung Association recommends two standard drug regimens for the treatment of TB: a combination of isoniazid (INH), rifampicin (RI) and pyrazinamide (PY) with or without ethambutol (EMB) and a combination of INH and RI with or without EMB. Of these agents, INH, PY and RI have been associated with liver toxicity. INH and PY are considered to be major hepatotoxins, whereas RI is considered to be relatively less hepatotoxic but is a powerful enzyme inducer, which may enhance the hepatotoxicity of INH (2).
Severe and sometimes fatal hepatitis associated with regimens containing INH, PY and RI has been well documented. Two cases were recently published of liver failure in patients receiving combination therapy with RI and PY for latent TB; one patient died (3).

The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) reviewed 420 suspected domestic reports of hepatobiliary adverse reactions associated with different combinations of INH, PY and RI that were received from the time of their introduction in Canada to May 18, 2001. (Each report may have contained more than one of the following reaction terms; however, each report was included only under the most important reaction term):

• INH alone: 258 reports of hepatic reactions (7 deaths).

• PY alone: 4 reports: 2 of hepatitis, and 1 each of hepatic failure and jaundice.

• RI alone: 27 reports: 12 of jaundice, 6 of hepatitis, 5 of abnormal liver enzyme levels, 3 of hepatocellular damage (1 death), and 1 of hepatomegaly.

• INH and PY: 1 report of hepatic failure (1 death).

• INH and RI: 110 reports: 50 of abnormal liver enzyme levels (1 death), 27 of hepatitis (2 deaths), 18 of jaundice (2 deaths), 9 of hepatocellular damage, 1 death), 2 each of hepatic failure and hepatomegaly, and 1 each of cholelithiasis and hepatic cirrhosis.

• RI and PY: 1 report of jaundice.

• INH, RI and PY: 19 reports: 7 of abnormal liver enzyme levels, 6 of hepatitis, 4 of jaundice and 1 each of hepatic coma and hepatic necrosis.

These reports suggest that liver toxicity may occur in patients receiving any of the drugs alone or in combination. The Canadian Tuberculosis Standards recommends baseline liver function testing when INH is used and regular monitoring only in patients who have pre-existing liver disease or a history of alcohol abuse or who are 35 years of age or older (1). The usefulness of liver function monitoring to detect fulminant liver failure is a controversial issue and needs to be further investigated. However, health care professionals are reminded that monitoring for liver toxicity (either through liver enzyme measurement or clinical monitoring) is important during treatment with any antitubercular regimen (2). It is essential to instruct patients to watch for symptoms suggestive of hepatitis (nausea, vomiting, stomach pain, lack of appetite, tiredness, dark urine or yellowing of the skin), and to stop taking their antitubercular medication and to consult their physician immediately if these symptoms occur (3).

References


Quality Assurance Issues

WHO pilot pre-qualification project for pharmaceutical products

It is recognized that low-cost drugs of assured quality have the greatest potential for maximizing efforts to combat major communicable diseases. As an integral part of their health care programmes and services, WHO and many other international agencies have traditionally been involved in the procurement and supply of drugs. More recently, a focus on access to drugs for HIV, malaria, and TB has become a priority at both international and country level and recent funding commitments by major industrialized countries articulate current efforts to address major public health concerns with determination and urgency.

In addition to the immediate problems of manufacture, provision and distribution, efforts to accelerate access to HIV-related drugs through generic competition have highlighted the complexities of assuring quality products in large-scale procurement programmes. Within such programmes, drugs are sourced from various manufacturers. However, at national level these drugs are not always subject to registration by a drug regulatory authority and subsequent assessment of quality is often lacking. Without quality assurance mechanisms, programmes risk supplying substandard, counterfeit and/or contaminated medicines, leading to product complaints and recalls, waste of precious funding and, more seriously, creating a potential health disadvantage to patients through administration of ineffective medicines.

Some organizations involved in procurement, including UN agencies, have devised their own quality systems but these have been developed independently. Additionally, although some agencies contract inspections at the site of manufacture, the extent and quality of these inspections varies according to the resources available. The establishment of harmonized procedures would render such inspections consistent, making mutual recognition and coordination possible. In short, uniform pre-qualification and quality assurance systems are essential for procurement agencies to function effectively.

Pilot project on procurement, quality and sourcing

As a matter of urgency, WHO and other UN agencies have begun to address these problems by setting up a plan to provide systems for the pre-qualification of manufacturers wishing to supply pharmaceutical products to international procurement agencies. Given the magnitude and ambitiousness of the task, the project is being implemented in a step-wise fashion covering:

- Pre-qualification of a certain number of manufacturers by WHO.
- Creation of unified procedures for performing inspections of suppliers prior to sourcing of pharmaceuticals.
- Evaluation of information on quality specifications of products submitted by suppliers.
- Creation of a model quality assurance system and pre-qualification procedures for use by procurement agencies.

Because of the overwhelming need to increase access to HIV drugs in those countries where the disease is now the leading cause of mortality, a pilot project will target manufacturers of pharmaceuticals for HIV/AIDS for WHO pre-qualification.

Important secondary outcomes are expected as a result of the pilot project. These include:

- pre-qualification by WHO for the procurement of drugs for other public health threats such as TB and Malaria.
- agreement among interested agencies on coordination of inspections, evaluation of product quality, training of inspectors, and mutual recognition of inspection reports, enabling resources to be saved and duplication avoided.
- strengthening of confidence in public health and enhanced patient compliance of treatments by assuring the quality of pharmaceuticals.
• strengthening of collaboration between WHO regional and country offices and drug regulatory authorities. Ongoing monitoring, review and modification of existing quality-related systems and programmes.

• establishing more effective networking and information exchange on drug regulatory and quality assurance issues.

Establishment of a quality assurance system for pre-qualification by WHO

A quality assurance system has been established by WHO for use in the pre-qualification of HIV drugs. Detailed procedures are set out in the *Operational Quality Manual*, covering product evaluation, site inspections, and related activities. The system covers good manufacturing practices, a code of conduct for inspectors, an inspection procedure, inspection report formats, standard operating procedures for inspectors, compilation of a product dossier, and guidance for evaluation of supporting documentation. These documents are published on the WHO HIV/AIDS Drugs Pre-qualification website (www.who.int/medicines) and are available from Quality and Safety: Medicines, Essential Drugs and Medicines, World Health Organization, 1211 Geneva 27, Switzerland.

Procedure for pre-qualification

Pre-qualification will involve evaluation of:

• Information provided by the supplier, manufacturer, and drug regulatory authorities.

• Production and quality control activities of the manufacturer.

• Product information submitted by manufacturers including formulation, manufacture, test data and results.

• Assessment of consistency in production and quality control through inspection of compliance with GMP.

• Random sampling and testing of drugs supplied.

• Storage and distribution of products.

• Handling of complaints and recalls.

• Complaints from agencies and countries.

**Essential requirements**

• The product must be manufactured in compliance with WHO GMP.

• Product certificates should be obtained in accordance with the *WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce*.

• Products must be of assured quality compliant with WHO guidelines.

• Specific ethical conditions determined by UN agencies should be complied with.

• Product data and information dossiers as set out on the following page.

Expression of interest

In the context of increasing access and affordability of HIV/AIDS-related care and treatment, WHO, in collaboration with UNICEF, UNAIDS, and UNFPA has invited expressions of interest (EOI) from manufacturers of pharmaceutical products used in the management of HIV-related diseases. This activity is also supported by the World Bank.

Manufacturers have been requested to submit EOIs and product dossiers for various dosage forms and strengths of products in the following categories:

**Non-nucleoside reverse transcriptase inhibitors**

nevirapine efavirenz
delavirdine

**Nucleoside reverse transcriptase inhibitors**

zidovudine didanosine
didanosine stavudine
zalcitabine abacavir
lamivudine

**Protease inhibitors**

saquinavir ritonavir
indinavir nelfinavir
amprenavir lopinavir + ritonavir

**Anti-infective drugs:**

*Antibacterial and antitubercular agents*

azithromycin clarithromycin
clindamycin ceftriaxone
cefixime ciprofloxacin
rifabutin
WHO has twice invited expressions of interest (EOI) in the international press and through the Internet (http://www.who.int/medicines) and will continue to do this as and when specific groups of products are identified for pre-qualification. Manufacturers should be committed to provide such products at preferential prices to developing countries.

Submission of product data and information dossiers
In addition to the essential requirements, information should be submitted either as described below or in the format of a standard dossier such as that prepared when requesting product approval by a drug regulatory authority.

1. For innovator products.

- A summary of product characteristics (SPC).
- Assessment report(s) issued by the respective drug regulatory authority.
- A WHO-type batch certificate from the manufacturer. In the event that packaging of the product is different from that approved by ICH drug regulatory authorities, stability testing data should also be submitted. If the formulation, strength, specifications, etc. are different from the product for which the WHO-type product certificate(s) was issued, arguments and/or data to support the applicability of the certificate(s) despite the differences should be submitted.

2. For other multisource (generic) products, the data and information to be submitted should be in conformity with that described in "Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products (WHO/DMP/RGS/98.5) published by WHO, and should include information on:

(a) Details of the product.
(b) Regulatory status in different countries.
(c) Active pharmaceutical ingredient(s) (API) data including:
   - Properties of the API
   - Route(s) of synthesis
   - Specifications
   - Pharmacopeial description or in-house specifications
   - Stability testing results
   - Sites of manufacture
(d) Finished product data including:
   - Formulation
   - Manufacturing procedure
   - Specifications for excipients
   - Specifications for the finished product
   - Container/closure system(s) and other packaging
   - Stability testing results
   - Container labelling
   - Product information
   - Patient information and package inserts
   - Justification for any differences to the product in the country or countries issuing the WHO-type certificate(s)
   - Interchangeability
   - Summary of pharmacology, toxicology and efficacy of the product
   - Sites of manufacture

Screening of dossiers
Each dossier is screened for completeness prior to evaluation. If incomplete, the manufacturer is requested to rectify this within a specified time period. In the event this is not complied with, the dossier will not be retained. Dossiers that are in compliance with the requirements of the WHO are retained for evaluation and the manufacturing site listed for an inspection.
Dossier evaluation
Dossiers are evaluated by a team of experts appointed by WHO with experience in pharmaceutical development, pharmaceutics, bioequivalence and related areas. Evaluators are drawn from drug regulatory authorities and appointed in accordance with established terms of reference and based on WHO guidelines to ensure uniformity of decisions. WHO is available to provide technical support to the evaluation when required. Evaluators are required to sign a confidentiality agreement and declaration that they have no conflict of interest.

Site Inspections
WHO is planning and coordinating inspections at the manufacturing sites to assess compliance with good manufacturing practices (GMP) as recommended by WHO. The inspection will be performed by inspectors appointed by WHO with regulatory experience in production, quality control, quality assurance and GMP. The inspectors will report their findings to WHO.

An inspector of the national drug regulatory authority will be invited to accompany the team to the manufacturing and testing facilities as part of the inspection team.

Report and outcome of the evaluation and inspection
The evaluators and inspection team(s) will finalize reports according to an established WHO format describing the findings and identifying any non-compliance with the WHO guidelines. This will be communicated to the manufacturers. If any additional information is required, or corrective action has to be taken, WHO will postpone its final recommendations until such information has been submitted and evaluated, or the corrective action verified.

Testing of samples
Random samples of pharmaceutical product(s) supplied by interested suppliers, will be taken for independent testing.

Pre-qualification results
Pre-qualification will cover only those product(s) indicated by the manufacturer in the EOI. Once WHO is satisfied that the product and manufacturing site meet the recommendations of WHO guidelines, the product and the manufacturer will be listed in the Pre-qualified Suppliers List.

The Pre-qualified Suppliers List will be published by WHO for use by procurement organizations, interested governments and related agencies for the purchase of pharmaceuticals. The List will be reviewed annually, published by WHO and made available on the WHO website. Activities related to WHO procurement and pre-qualification will be carried out by independent units.

References

Antimicrobials have been used in food animals in North America and Europe for nearly half a century. Among the most common are drugs that are either identical to or related to those administered to humans, including penicillins, tetracyclines, cephalosporins (including ceftriaxone, a third-generation cephalosporin), fluoroquinolones, avoparcin (a glycopeptide that is related to vancomycin), and virginiamycin (a streptogramin that is related to quinupristin-dalfopristin). These antimicrobial agents are given to food animals as therapy for an infection or, in the absence of disease, for subtherapeutic purposes with the goals of growth promotion and enhanced feed efficiency and improved nutritional benefits of the animal feed (1).

There is considerable controversy about the amounts of antimicrobials that are given to food animals relative to the amounts given to humans, since manufacturers are not required to provide precise production figures. One estimate is that 50% of all antimicrobials produced in the United States are administered to animals, mostly for subtherapeutic uses. The Union of Concerned Scientists recently estimated that, each year, 24.6 million lb (11.2 million kg) of antimicrobials are given to animals for nontherapeutic purposes and 2 million lb (900,000 kg) are given for therapy; in contrast, 3 million lb (1.3 million kg) are given to humans (2). Whichever figures are accepted, it is fair to state that substantial amounts of antimicrobials are administered to food animals for growth promotion and feed efficiency in the absence of known disease.

An intense debate has raged over the past three decades on the impact on health in humans of the use of antimicrobial agents in food animals. Three reports have now been published (3–5) which add weight to the rising movement to ban subtherapeutic uses of antimicrobials in animals. In one study, 20% of samples of ground meat obtained in supermarkets were found to be contaminated with salmonella and 84 percent of the isolates were resistant to at least one antimicrobial (3).
The use of antimicrobials in food animals selects for resistant strains and enhances their persistence in the environment. Drug resistance in salmonella and campylobacter can increase the frequency and severity of infections with such organisms, limit treatment options, and raise health care costs. These effects may be related to enhanced shedding and augmented virulence of resistant strains, increased rates of transmission of these strains, and the ineffectiveness of initial regimens of antimicrobial therapy against such strains. The risk of infection with a resistant strain of salmonella or campylobacter is increased when a person has taken an antimicrobial within a few weeks before the exposure.

Another concern is the horizontal spread of the resistance genes from bacteria in food animals to commensal strains in the intestinal microflora of humans. Extensive transfer of antimicrobial-resistance genes has been demonstrated among enteric bacteria, bacteroides, and Gram-positive bacteria in the human colon (7). These organisms serve as a reservoir of resistance genes that can be transferred to other members of the microflora or to pathogenic bacteria. Not all antimicrobial resistance in human pathogens can be ascribed to the use of these drugs in food animals, however. The use of antimicrobials in humans, much of which is inappropriate, is responsible for rising levels of resistance in organisms such as *Streptococcus pneumoniae, Staphylococcus aureus,* and *Neisseria gonorrhoeae,* as well as in many bacteria acquired in hospitals.

The same may apply to vancomycin-resistant enterococci, which currently account for 25 percent of nosocomial enterococcal infections in the United States. In some European countries, the rates of carriage of vancomycin-resistant enterococci in the general population range from 12 to 28 percent; yet in most European hospitals the incidence of infection with these organisms remains very low. The opposite situation prevails in the United States. As reported (4), the rate of carriage of vancomycin-resistant enterococci in the general population is one percent, whereas nosocomial infections with vancomycin-resistant enterococci are widespread in many hospitals in the United States. The epidemiologic characteristics of vancomycin-resistant enterococci in the United States indicate that acquisition within a hospital, particularly in an intensive care unit, and prior use of certain antimicrobial drugs are risk factors for infection (8). Although the transmission of vancomycin-resistant enterococci in the United States has not been related to the use of antibiotics in food animals, the increasing burden of resistant *E. faecium* in the food chain (4) and the ability of these strains to colonize the human intestine (5) represent a potential threat.

The most widely proposed argument in favor of the use of antimicrobials for growth promotion and feed efficiency in animals is economic savings. However, there are alternatives, as shown in Europe after the use of these drugs was abandoned. The economic losses could be minimized and even neutralized by improvements in animal husbandry, the quality of feed, and hygiene. On the basis of discussions by an expert committee of the Alliance for the Prudent Use of Antibiotics, several recommendations can be made.

- Antimicrobials should be used only when indicated in individual infected animals for a targeted pathogen and prescribed by a veterinarian.
- The use of certain drugs that have important uses in humans, such as fluoroquinolones and third-generation cephalosporins, should be prohibited in animals.
- Finally, the subtherapeutic use of these agents to promote growth and feeding efficiency should be banned — a move that would decrease the burden of antimicrobial resistance in the environment and provide health-related benefits to both humans and animals.

References


**Declaration of Helsinki and placebo-controlled clinical trials**

The Declaration of Helsinki is acknowledged as the cornerstone of research ethics. Its current guidelines on the ethical use of placebo-controlled trials has caused some confusion in the research world and for this reason the Council of the World Medical Association has decided to publish a note of clarification on their interpretation. This step was necessitated by the cancellation of the Fifty-third World Medical Association General Assembly, which was due to take place during October 2001. The Assembly is the only body with the authority to adopt formal changes to the Declaration. The full text of the note reads as follows.

The WMA is concerned that paragraph 29 of the revised Declaration of Helsinki (October 2000) has led to diverse interpretations and possible confusion. It thereby affirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic methods, or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

At the same meeting, the WMA decided to appoint a panel of advisers, representative of all stakeholders in research, to assist the WMA in its continuing review of the Declaration of Helsinki.

**Reference**: http://www.wma.net/e/home.html
General Information

Improving the quality and usefulness of drug regulatory authority websites

The Internet can be a valuable resource for users seeking health information. For most patients, health professionals, policy makers and pharmaceutical companies, the website of the national drug regulatory authority should be the most appropriate place to obtain independent information on products. By having a reliable, easy to use, accessible and up-to-date website, a drug regulatory authority can increase its efficiency and efficacy and will be seen as being more transparent in its work. Given the need to make more information available, particularly on regulatory action, it has been suggested that a WHO model website for drug regulatory authorities should be created to support the availability of reliable, good quality information. Because this information could potentially affect health outcomes for millions of people, there is also a growing urgency for objective, reproducible criteria that can be used to harmonize, develop and evaluate the quality of such websites.

WHO model website

While health information proliferates on the Internet and e-trade increases worldwide, there is a growing need for health professionals and patients to have access to reliable, independent information on pharmaceutical products. Provision of information, including laws and regulations, helps to maintain public confidence in the work of regulatory authorities and pharmaceutical products in general.

In order to respond to this need, WHO has undertaken to develop a model website for use by drug regulatory authorities wishing to create their own website or improve an existing one. Before development of the project could begin, the most important pieces of information that a drug regulatory authority website should contain were identified in a list of objective, reproducible criteria designed to serve as the gold standard for the analysis. An assessment was then made of the quality of information currently contained on existing websites in different languages and regions and at different levels of sophistication. Those countries having a drug regulatory authority website were identified through a search of the Internet or contacting the national or drug regulatory authority in each country.

In parallel, a bibliographic search was carried out on assessments of health information websites. A set of key criteria was developed relevant to WHO priorities and policies on health information which included different types of drug information. Criteria were identified and a scoring system was devised to weigh content, links, interactivity, accessibility and target user balance (2).

General criteria

User friendliness: First impression and general appearance is most important when accessing a Website. Pages should be designed attractively and entice further exploration; information should be presented logically and clearly enough to be successfully manipulated by the intended users. Information should be easy to find and available in the national and, whenever possible, another widely used language for international users.

Site map: A good map will indicate logical links and organization of the site; it explains how to navigate through pages and indicates where to go and how to get there.

Navigability: This is the characteristic that allows a user to obtain effectively important information. Accessibility, logical organization, and internal search engines are essential.

Speed: The home page and subsequent links (except those from websites outside the control of the regulatory authority) should be displayed within 4 to 5 seconds.
Search: The site should have its own search engine, which also permits a search or hyperlink to other sites.

Update: The website should state the date on which it was created and when last updated. The site is regularly reviewed.

Specific criteria
Mission statement: The mission statement and purpose of the drug regulatory authority is clearly stated and easily accessible. Activities and programmes are described.

Contact information: Contact information with names, addresses, telephone, fax and e-mail should be readily available, complete and up-to-date for each activity. A responsible person or service should be identified to obtain further information.

Organizational structure: The structure of the drug regulatory authority should be available, complete and up-to-date. It allows information on each department to be obtained by selection.

Services: The site offers information related to the drug regulatory authority. The data are clearly organized and easily understood by the users. The site does not contain language which is persuasive, but informative.

News, events and meetings: The site should mention and describe news, events, and planned meetings and has a calendar which is regularly updated.

Safety alerts: Patient and health professionals have easy access to safety alerts by date and product name: information covers recalls, suspensions, revocations, recalls (batch is also mentioned), withdrawals, Dear Dr Letters and labelling changes. The information should be comprehensive, detailed, and chronological.

Adverse drug reactions (pharmacovigilance): The site contains a definition of terms, the procedure for reporting of adverse drug reactions and adverse drug events, how to report on-line, links to useful sites, latest pharmacovigilance reports, etc.

Feedback form: A facility should be available for enabling any user to contact the agency, either to ask questions or to report problems. This feedback form should be complete, easy to download and send back to the regulatory authority.

Regulatory guidance on legislation and regulations: Guidance, including laws, decrees, orders and any legislative and regulatory material related to pharmacy, drug manufacturing, drug registration process, commerce, information on promotion and advertising or e-trade, including the WHO ethical criteria for medicinal drug promotion, should be available.

Instructions for marketing applicants: Information for applicants should be present with a sufficient degree of detail to assist the preparation of registration dossiers, composition of the file, list of documents to file for a first submission, variations, renewal, extension, transfer of marketing authorization. Information on fees, norms, standards and guidance for pharmaceutical production, drug registration and accelerated approval procedures. Information on drug regulation and quality assurance systems, drug regulatory information, guidelines for good clinical practice (GCP) for trials on pharmaceutical products, etc.

Forms which can be downloaded: These should include, among others, a marketing authorization or clinical trial application form, variation application form, and template of summary of product characteristics.

Medicinal products (human/veterinary medicines): This criteria is most important. The website should include:

- The list of drugs authorized in the country, including the generic name, presentations (dosage form and strength), patient information leaflets, summary of product characteristics, labelling, etc.
- A search facility, which permits the user to find items either by brand name, marketing authorization holder, INN/generic name, or therapeutic group.
- The list of cancelled marketing authorizations.
- Information on orphan drugs.
- Products under special postmarketing surveillance.

Approved manufacturers: Information on manufacturers in the country should be presented and easily readable. A list of approved manufacturers — name, address, contact, licence status, last inspection date, etc should be available. Charts or graphics should enhance information rather than distract from it.
Import and export: Statistics on import and export, guidance for importers, exporters, and the WHO type certificate, should be presented and easily readable.

Approved wholesalers, distributors, pharmacies: A list of approved wholesalers, distributors, pharmacies with information on activities and volume of business should be presented.

Basic statistics on drug consumption: The site should offer information covering:

- Global consumption data.
- Quantity of packages sold in pharmacies.
- Consumption at hospitals.
- Data on OTC sales.
- Quantity of drugs produced, etc.

Basic statistics on country profile: The site should contain information such as the pharmaceutical market size.

Basic statistics on drug regulatory authority activities: The number of new drug applications received, pending applications, time taken to process applications, positive or negative decisions, applications withdrawn, inspections of pharmacies, wholesalers, manufacturing sites, etc.

Links: Hyperlinks to other pages and sites should be:

- Worthwhile and appropriate for the intended audience.
- Clearly labelled and serve an easily identifiable purpose.
- Of added value to the Website.
- Current and operating efficiently.
- Grouped in some type of logical order.

Links related to medical journal Websites, national drug regulatory authorities, and international links should be accessible.

Publications:

- Sources of information cited should be reliable, pertinent and identified.
- Publications should be downloadable with a bibliographic list of references which is current.

The publications page should contain, for example, the annual report, quarterly report, cumulative list of recalls, safety alerts, and other decisions that restrict use of medicinal products. Guidance materials, latest list of approved products, latest list of approved manufacturers, wholesalers, importers, distributors, medical journals, newsletter and periodicals, etc.

Conclusions

Very few drug regulatory authorities offer their information resources via a website to an Internet audience. Indeed, many drug regulatory authorities do not have a website, and those that have one seem to have either a very small amount of information, or a vast amount of information which is difficult to access. Most websites do not post independent drug information, and very few provide access to drug marketing authorizations or approved drug information. The quality of health information provided is very heterogeneous and could benefit from improvement.

Without drug information, health-care providers and consumers may be uncertain as to which drugs are approved for treating conditions, which drugs meet national regulations and which drugs may be imported. For consumers, problems are exacerbated by the growth in pharmaceutical e-trade, which is unregulated. Ensuring rational use of drugs and efficient drug supply in this situation becomes even more difficult. At the same time, lack of drug information can suggest that drug regulatory authorities are not “transparent” enough, ultimately leading to poor trust in the quality and legitimacy of their work.

Drug regulatory authorities should provide reliable drug information for consumers/patients, health professionals, public and private sector organizations (hospitals, manufacturers, importers etc.), making it more available and easily accessible. The Internet is a powerful information tool that has proved to be a source of valuable, good quality information on approved drugs, treatments and medical products available on different national markets.
**Outcome of website review:**

- Only 13.7% scored ‘good’ on information on medicinal products.
- Only 11.8% scored ‘good’ on safety information.
- Only 7.8% scored ‘good’ on drug consumption information.
- No feedback form was provided for contacting or informing the authority in 56.9% of the websites.
- 54.9% had no recent update of their web page (during the current year).
- 56.9% had no text search, or this was not functioning.
- 58.8 % had no publications mentioned at all.
- The links function scored ‘inadequate’ in 51% of the websites assessed. Also, services were rated inadequate in 71.4%, although this score may be considered subjective.
- 27.5% have a good site map, but 60.8% have no site map at all.
- 27.5 % have good pages on news and events, 52.9% have nothing related to such topics.
- The “best results” were found for speed (56.9%), navigability (58.8%), contact information (37.3%) and organizational structure (41.2%).
- 47.1% provided good instructions for website visitors.
- Results showed that mission statements (51%), user friendliness (49%) and regulatory guidance on legislation (39.2%) were not given enough attention.

*A scoring system was used ranging from 0 to 2*  
(0 = inadequate, 1 = intermediate 2 = good) to weigh each criteria.

**Future activities**

The criteria set out in this article were developed by WHO and presented to drug regulatory officials and representatives of nongovernmental organizations as part of the work towards creation of a WHO model website. It is intended that the model website will be pre-configured with WHO Guidelines and working data, with the minimum set of information to be defined that is related to the core functions of a drug regulatory authority, as far as confidentiality rules and data security allow.

As part of the project, WHO will assist a selected number of interested countries in establishing a Website based on the WHO model. At a future stage, the model Websites will be validated through a panel of users from different stakeholders.

The benefits that drug regulatory authorities will gain from the model Website initiative will contribute to:

- Increasing the transparency of their own activities.
- Improving collaboration between drug regulatory authorities, health professionals and academics.
- Improving the public health impact of drug regulatory work.
- Facilitating networking between drug regulatory authorities to solve drug regulation problems.
- Offering reliable and unbiased drug information to guide Internet users.
Additionally, increased availability of drug regulatory information will combat substandard and counterfeit drugs by enabling verification of product registration status in countries and alert drug regulators and health care providers to regulatory action in other countries.

References


## Drug Regulatory Authority Websites

### Africa – 4 of 49 countries (8.5%)
- Algeria: [http://www.ands.dz/](http://www.ands.dz/)

### The Americas – 7 of 36 countries (19.5%)
- United States of America: [http://www.fda.gov/](http://www.fda.gov/)

### The Eastern Mediterranean

### Europe – 28 of 51 countries (excluding EMEA) (55.8%)
- Austria: [http://www.bmsg.gv.at/](http://www.bmsg.gv.at/)
- Belgium: [http://www.afigp.fgov.be](http://www.afigp.fgov.be)
- Bulgaria: [http://www.bda.bg/](http://www.bda.bg/)
- Denmark: [http://www.dkma.dk/](http://www.dkma.dk/)
- Finland: [http://www.narn.fi/](http://www.narn.fi/)
- Germany: [http://www.bfarm.de/gb_ver/](http://www.bfarm.de/gb_ver/)
- Ireland: [http://www.imb.ie/](http://www.imb.ie/)
- Italy: [http://www.sanita.it/farmaci/](http://www.sanita.it/farmaci/)
- Lithuania: [http://www.vvkt.lt/ENG/default.htm](http://www.vvkt.lt/ENG/default.htm)
- Luxembourg: [http://www.etat.lu/MS/DPM/fr/fr_index.html](http://www.etat.lu/MS/DPM/fr/fr_index.html)
- Poland: [http://www.il.waw.pl/eng/version.htm](http://www.il.waw.pl/eng/version.htm)
- Slovakia: [http://www.sukl.sk/sukl_en.htm](http://www.sukl.sk/sukl_en.htm)
- Sweden: [http://www.mpa.se/ie_index.html](http://www.mpa.se/ie_index.html)
- Switzerland: [http://www.lks.ch/default_E.asp](http://www.lks.ch/default_E.asp)
- Norway: [http://www.legemiddelverket.no/eng/reg/regulatory.htm](http://www.legemiddelverket.no/eng/reg/regulatory.htm)

### South-East Asia – 3 of 10 countries (30%)
- India: [http://www.mohfw.nic.in/kk/95/ia/toc.htm](http://www.mohfw.nic.in/kk/95/ia/toc.htm)
- Thailand: [http://www.fda.moph.go.th/enginfo.htm](http://www.fda.moph.go.th/enginfo.htm)

### Western Pacific Region – 9 of 28 countries (32.1%)
- Japan: [http://www.mhlw.go.jp](http://www.mhlw.go.jp)
Infliximab and congestive heart failure

United States of America — The manufacturer of infliximab (Remicade®) has issued a warning concerning new safety information. Infliximab is a biological therapeutic product indicated for the treatment of rheumatoid arthritis and Crohn disease.

Following a recent clinical trial in 150 patients with moderate to severe congestive heart failure, higher incidences of mortality and hospitalization for worsening heart failure were seen in patients treated with infliximab, especially those treated with the higher dose of 10 mg/kg. Seven of 101 patients treated with infliximab died compared to no deaths among the 49 patients on placebo. In this trial, stable but symptomatic patients with moderate to severe congestive heart failure were treated with 3 infusions of infliximab — 5mg/kg, 10 mg/kg or placebo, over 6 weeks.

For patients with rheumatoid arthritis or Crohn disease being considered for therapy with infliximab, do not initiate therapy in patients with congestive heart failure.

Patients with congestive heart failure currently receiving chronic infliximab treatment for rheumatoid arthritis or Crohn disease should be re-evaluated. Treatment should be discontinued in patients whose congestive heart failure is worsening; treatment discontinuation should be considered in patients with stable concomitant congestive heart failure.


Infliximab: warning of opportunistic infections

United States of America — The manufacturer of infliximab (Remicade®) has issued a warning concerning new safety information. Infliximab is a biological therapeutic product indicated for the treatment of rheumatoid arthritis and Crohn disease.

Tuberculosis and other serious opportunistic infections including histoplasmosis, listeriosis, and pneumocystosis have been reported in both clinical research and post-marketing surveillance. Some of the infections have been fatal. Accordingly a boxed warning has been added to the labelling for the product.

Between 24 August 1998 and 30 June 2001, 84 cases of tuberculosis were reported worldwide, with 14 cases of death. Most cases of tuberculosis were diagnosed within seven months of initiation of infliximab therapy and most reported use of concomitant immunosuppressive medications. An increased risk of infections associated with tumour necrosis factor (TNF) blockade, is consistent with the known effects of TNF on macrophage activation and granuloma formation. Thus far, approximately 170,000 patients have been treated worldwide with infliximab.

For patients who have resided in regions where histoplasmosis is endemic, the benefits and risks of infliximab treatment should be carefully considered before initiating therapy.


Brimonidine ophthalmic drops: accidental ingestion

Canada — Accidental oral ingestion of brimonidine ophthalmic drops (about 2 mL) in a 28-month-old child caused decreased consciousness and apnea.
resulting in intubation, ventilation and surveillance in an intensive care unit for 40 hours. Recommendations for child-resistant packaging were made to the manufacturer. As an immediate option to reduce the risk of accidental exposure, consider dispensing these ophthalmic drops in childproof vials.


P-Glycoprotein and drug interaction

Australia — Several published reports are available of cases in which a macrolide antibiotic has increased blood concentration of digoxin. It is now known that digoxin is transported by P-glycoprotein — perhaps better known for causing multidrug resistance in malignant tumours but also a drug transporter pump in the gut and kidneys and many other organs. P-glycoprotein in the gut pumps a drug back into the gut lumen, therefore, if the pump is inhibited, the result will be an increase in concentration of the substrate drug in the body.

The Adverse Drug Reactions Advisory Committee has received 2 reports of digoxin toxicity occurring in patients given roxithromycin. Both cases are consistent with roxithromycin inhibiting P-glycoprotein and hence increasing the net amount of absorption from the gut and reducing the renal excretion of digoxin. Both patients were on a dose of 250 µg digoxin daily.

Many, but not all, of the drugs which are transported by P-glycoprotein are also metabolized by cytochrome P4503A4 which can confuse the interpretation of interactions. This is not a problem with digoxin. Other common substrates for P-glycoprotein are cyclosporin, fluoroquinolones, HIV-protease inhibitors, lignocaine, quinidine and ranitidine. Common inhibitors are diltiazem, verapamil and macrolide antibiotics. Prescribers should be aware of the potential for interactions caused by this mechanism.


Nonacog alfa: intensive surveillance

European Union — The Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) has recommended intensive post-market surveillance for all new patients treated with nonacog alfa, human recombinant factor IX (BeneFIX®), as well as the initiation of two new clinical trials. The recommendations have been made following a good clinical practice (GCP) inspection of two of the three pivotal clinical studies on which the marketing authorization is based.

Nonacog alfa has been commercially available in the United States since 1997 and in Europe since 1999. Post-marketing data since then support the safety and efficacy profile of the product. The CPMP considers that the benefit/risk balance of nonacog alfa for the treatment and prophylaxis of bleeding in previously treated patients with haemophilia B is positive, based on the data presently available. However, these are insufficient to be certain of the frequency of some adverse drug reactions, especially those linked to inhibitor formation and to allergic reactions.

Patients treated with nonacog alfa may continue their therapy. However, patients who experience suspected adverse reactions should be monitored carefully and the risk/benefit of continued treatment should be evaluated. In the case of severe allergic reactions, alternative haemostatic measures should be considered. To date, there are insufficient data to recommend the use of nonacog alfa in children less than 6 years of age and to provide information on inhibitor incidence in previously untreated patients.


Tenofovir disoproxil fumarate approved for HIV infection

United States of America — The Food and Drug Administration has approved Viread® (tenofovir disoproxil fumarate), a new antiviral drug indicated for treatment of HIV-1 infection in combination with other antiretroviral medicines. Tenofovir disoproxil fumarate is the first nucleotide analogue approved for HIV-1 treatment. Nucleotides are similar to nucleoside analogues, and block HIV replication in the same manner.

The introduction of potent antiviral drugs and the combined use of these drugs has markedly reduced replication of HIV in many patients and has im-
proved survival rates. Yet because HIV mutates rapidly, resistance to one or more of these potent drugs may develop over time, necessitating the development of new drugs to treat these resistant virus strains.

FDA based its approval of tenofovir disoproxil fumarate on two clinical studies involving more than 700 patients who had previously been treated with antiretroviral agents, but showed signs of continued HIV replication despite drug therapy. Because the approval of tenofovir disoproxil fumarate was based on clinical trials involving patients who were previously treated with antiretrovirals, the risk-benefit ratio for untreated patients has yet to be determined. Furthermore, there are no study results to show long-term inhibition of the clinical progression of HIV by tenofovir.

The most frequently reported adverse events among patients in the clinical trials were mild to moderate gastrointestinal problems including diarrhea, nausea, vomiting and flatulence. Lactic acidosis and hepatomegaly with steatosis (severe liver enlargement and excess fat in the liver) have also occurred among patients treated with nucleoside analogues alone, or in combination with antiretrovirals.


Ciprofloxacin hydrochloride for inhalation anthrax

Ciprofloxacin hydrochloride is indicated for inhalational anthrax (post-exposure), to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*. Drug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized *Bacillus anthracis* spores (1).

Ciprofloxacin reduces the risk of severe disease following exposure, but does not prevent exposure to aerosolized Bacillus anthracis. If a person is exposed to *B. anthracis*, the risk of adverse events caused by ciprofloxacin hydrochloride therapy may be acceptable because of the severity of this disease. However, in the absence of exposure, the risk of side effects may not be acceptable. Possible adverse events and other concerns include:

- Drug Interactions. Ciprofloxacin may increase levels of theophylline and caffeine, other vitamin and drug products may reduce availability of ciprofloxacin.
- Hypersensitivity.
- Pseudomembraneous colitis.
- Tendonitis/ tendon rupture.
- Photosensitivity.

Use of an antibiotic inappropriately (for example when exposure has not been confirmed) can lead to the emergence of resistant strains of bacteria. The usefulness of ciprofloxacin hydrochloride as an antibiotic may be lost if widespread use occurs. The safety and effectiveness of ciprofloxacin in patients less than 18 years of age is not established except for post-exposure use in inhalational anthrax. Ciprofloxacin causes arthropathy in juvenile animals.

Fluroquinolones are not generally recommended during pregnancy because of their known association with arthropathy in adolescent animals. However, animal studies have not shown evidence of teratogenicity related to exposure to ciprofloxacin (2). A 1999 consensus statement by the Working Group on Civilian Biodefense recommends that ciprofloxacin be used at usual adult doses in pregnant women for therapy and postexposure prophylaxis following anthrax exposure (3).

References

1. http://www.fda.gov/cder/drug/infopage/ or through: druginfo@cder.fda.gov


DTPa and limb swelling

Australia — The replacement of the whole cell pertussis antigens (Pw) with acellular pertussis antigens (Pa) in the combination diphtheria, tetanus and pertussis vaccines (DTPa) (Infanrix®,
Tripacel® has been an important recent development. Clinical studies have shown that DTPa causes fewer worrying reactions like inconsolable crying, high fevers, hypotonic-hyporesponsive episodes and convulsions than DTPw (1).

As clinical experience with the use of DTPa-containing vaccines has grown, it has been observed that there is an increase in the rate of occurrence and severity of injection site reactions with each successive dose (2). The fourth and fifth doses of DTPs sometimes cause extensive limb swelling which may be associated with redness and pain. These booster doses are recommended at 18 months (fourth dose) and four years (fifth dose) in Australia and may be given into the arm or the thigh. Of the 331 Australian reports of suspected adverse reactions to DTPa vaccines received between late November 1997 and mid-June 2001, 103 described injection site reactions in children aged 18 months or older. In contrast, only 37 described similar reactions in younger children. Of the 103 reports in the older children, forty-eight described extensive limb swelling or included measurements of the swelling with at least one dimension greater than 10 cm. Descriptions like “swollen, red, hot from groin to ankle” and “arm swollen from elbow to shoulder” are typical.

Based on the children’s ages, 37 of the reports are likely to relate to a fourth dose of DTPa and 11 to a fifth dose. The possibility of these reactions is mentioned in the Australian product information for the vaccines. This reporting needs to be seen in the context of approximately 250,000 Australian children eligible each year for either a fourth or fifth dose of DTPa. The estimated frequency of extensive limb swelling after booster doses of DTPa is about 2% (1). The frequency of extensive limb swelling with whole cell pertussis-containing vaccines (DTPw) is less well documented, but in one recent study was also 2% (2). Extensive local reactions involving most of the upper arm or thigh have also been described following booster doses of diphtheria-tetanus vaccine (DT) which does not contain pertussis (3). It has been proposed that DTPs-associated extensive limb swelling reactions occur more commonly with those vaccines which contain larger amounts of diphtheria antigens, but further study is needed.

In the forty-eight reports of extensive limb swelling reactions to DTPa, the outcome was “unknown” for 7 reports and “not yet recovered” for 14 reports. In all the other reports the child was said to have recovered without sequelae. This is consistent with a published report of twenty cases of swelling all of which subsided spontaneously, completely and without sequelae (2). To date there is insufficient information available about whether a child who has experienced extensive limb swelling after the fourth dose of DTPa would be likely to have a similar reaction to a fifth dose at four years of age.

DTPa generally causes far fewer local reactions than DTPw, but extensive limb swelling seems to occur with both vaccines with equal frequency. Parents should be warned of this possible adverse reaction. As the swelling resolves without sequelae, and pertussis continues to circulate in the community, it is recommended that a child who develops extensive limb swelling after a fourth dose of DTPa be offered a fifth dose of DTPa, with appropriate informed parental consent. This recommendation is endorsed by the Australian Technical Advisory Group on Immunization (ATAGI).

References


Nitrofurantoin and peripheral neuropathy

Australia — A recent letter to the Medical Journal of Australia has highlighted a case of peripheral neuropathy in association with nitrofurantoin, an antibiotic used for urinary tract infection prophylaxis (1). This is a well known effect of nitrofurantoin but awareness may be declining due to reduced use.

The Australian Adverse Drug Reactions Committee (ADRAC) has received 18 reports of peripheral neuropathy since 1978. While there were no reports received between 1990 and 1997, there have been three in the last 4 years. Most of the reports have involved elderly females. Daily dosages have ranged from 100 mg to 400 mg with a median of 250 mg. The time to onset has ranged from 3
Peripheral neuropathy can be both severe and irreversible.

Prescribers should take care with the use of nitrofurantoin in the elderly, those with renal impairment and those taking the drug for prolonged periods. Particular attention to the use of the minimum effective dose may reduce the possibility of occurrence of peripheral neuropathy and any suggestive symptoms should trigger cessation of the drug.

Reference:

**Continued suspension for tolcapone**

European Union — Tolcapone (Tasmar®) was marketed in August 1997 for the treatment of Parkinson disease in 100 mg and 200 mg film-coated tablets.

In November 1998, the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) recommended suspension of tolcapone following reports of severe hepatotoxicity. Subsequently, the suspension was renewed in October 2000.

In September 2001, evidence was reviewed and the benefit/risk profile re-assessed and the CPMP have recommended renewal of the suspension for a further year pending the results of an ongoing prospective trial on comparable treatments.


**MMR vaccine and idiopathic thrombocytopenic purpura**

United Kingdom — Thrombocytopenia is a well-recognized rare adverse reaction with measles, mumps, rubella (MMR) vaccine which is listed in the product information.

A recently published study conducted by the Public Health Laboratory Service has found the absolute risk of a child developing idiopathic thrombocytopenic purpura (ITP) within 6 weeks of the first dose of MMR to be 1 in 22,300 cases with 2 out of every 3 cases being attributable to MMR (1).

The Committee for Safety of Medicines has recommended:

- Children who developed ITP within 6 weeks of the first dose of MMR (or its component vaccines should have their serological status evaluated before the second dose is due. If serology testing suggests that a child is not fully immune against measles, mumps and rubella then a second dose of MMR is recommended.

- The Public Health Laboratory Service are offering a free serological testing service for children developing ITP within 6 weeks of the first dose of MMR.


**New communications and networking unit at EMEA**

European Union — The European Agency for the Evaluation of Medicinal Products (EMEA) has announced the creation of a new unit with responsibility for facilitating communications and networking between the Agency’s partners. This will reinforce the networking character of the EMEA by focusing on communication tools and IT systems needed to bring the Agency closer to the 27 different competent authorities in Member countries. The IT systems will allow secure regulatory exchange between authorities and industry during submission and evaluation of medicines.

The following final anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 21 October 2001. They are included in the January 2002 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, e-mail: whocc@nmd.no.

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

- Agents used in photodynamic therapy
- Bone morphogenetic proteins

**New ATC 5th level codes:**

- acetyldigoxin combination C01AA52
- agalsidase alfa A16AB03
- agalsidase beta A16AB04
- amlexanox A01AD07
- anakinra L04AA14
- arsenic trioxide L01XX27
- ascorbic acid G01AD03
- ascorbic acid S01XA15
- bisoxatin A06AB09
- BMP-2 M05BC01
- BMP-7 M05BC02
- cilnidipine C08CA14
- crilanomer D03AX09
- darbepoetin alfa B03XA02
- denileukin diftitox L01XX29
- dienogest and estrogen G03FA15
- diflucortolone D07XC04
- dimethyl sulfoxide G04BX13
- drotrecogin alfa (activated) B01AD10
- esomeprazole, amoxicillin and clarithromycin A02BD06
- fomepizole V03AB34
- formoterol and other drugs for obstructive airway diseases R03AK07
- fulvestrant L02BA03
- gadobutrol V08CA09
- hemoglobin raffimer B05AA09
- imatinib L01XX28
- insulin glargine A10AE04
New ATC 5th level codes:

- levocetirizine R06AE08
- lutropin alfa G03GA07
- methyl aminolevulate L01XD03
- monobenzone D11AX13
- multienzymes and acid preparations A09AC02
- omalizumab R03DX05
- phloroglucinol A03AX12
- rupatadine R06AX28
- sodium selenite A12CE02
- sodium tartrate A06AD21
- tacrolimus D11AX14
- talinolol C07AB13
- tegafur, combinations L01BC53
- thioacetazone, combinations J04AM04
- tiotropium bromide R03BB04
- unoprostone S01EX04
- vaginal ring with progestogen and estrogen G02BB01
- zinc acetate, basic A16AX05

ATC code changes

- Previous: porfimer sodium L01XX15
- New: porfimer sodium L01XD01
- Previous: verteporfin L01XX26
- New: verteporfin L01XD02
- Previous: alginic acid A02EA01
- New: alginic acid A02BX13
- Previous: silicones A02DA01
- New: silicones A03AX13

ATC name changes

- Previous: Antacids, drugs for treatment of peptic ulcer and flatulence
- New: Drugs for acid related disorders A02
- Previous: Drugs for treatment of peptic ulcer
- New: Drugs for peptic ulcer and gastroesophageal reflux disease (GORD) A02B
- Previous: Other drugs for treatment of peptic ulcer
- New: Other drugs for peptic ulcer and gastroesophageal reflux disease (GORD) A02BX
- Previous: Other antacids, drugs for treatment of peptic ulcer and flatulence
- New: Other drugs for acid related disorders A02X
- Previous: Antispasmodic and anticholinergic agents and propulsives
- New: Drugs for functional gastrointestinal disorders A03
- Previous: Synthetic antispasmodic and anticholinergic agents
- New: Drugs for functional bowel disorders A03A
- Previous: Other synthetic anticholinergic agents
- New: Other drugs for functional bowel disorders A03AX
- Previous: Drugs affecting mineralization
- New: Drugs affecting bone structure and mineralization M05B
- Previous: Anti-asthmatics
- New: Drugs for obstructive airway diseases R03
- Previous: Adrenergics and other anti-asthmatics
- New: Adrenergics and other drugs for obstructive airway diseases R03AK
- Previous: Epinephrine and other anti-asthmatics
**ATC name changes**

*New:* Epinephrine and other drugs for obstructive airway diseases  
*Previous:* Isoprenaline and other anti-asthmatics  
*New:* Isoprenaline and other drugs for obstructive airway diseases  
*Previous:* Fenoterol and other anti-asthmatics  
*New:* Fenoterol and other drugs for obstructive airway diseases  
*Previous:* Salbutamol and other anti-asthmatics  
*New:* Salbutamol and other drugs for obstructive airway diseases  
*Previous:* Repoterol and other anti-asthmatics  
*New:* Repoterol and other drugs for obstructive airway diseases  
*Previous:* Salmeterol and other anti-asthmatics  
*New:* Salmeterol and other drugs for obstructive airway diseases  
*Previous:* Other anti-asthmatics, inhalants  
*New:* Other drugs for obstructive airway diseases, inhalants  
*Previous:* Other anti-asthmatics, inhalants  
*New:* Other drugs for obstructive airway diseases, inhalants  
*Previous:* Adrenergics and other anti-asthmatics  
*New:* Adrenergics and other drugs for obstructive airway diseases  
*Previous:* Other anti-asthmatics for systemic use  
*New:* Other systemic drugs for obstructive airway diseases  
*Previous:* Other anti-asthmatics for systemic use  
*New:* Other systemic drugs for obstructive airway diseases

**New DDDs:**

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>DDD</th>
<th>Unit</th>
<th>Route of Administration</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>almotriptan</td>
<td>12.5</td>
<td>mg</td>
<td>O</td>
<td>N02CC05</td>
</tr>
<tr>
<td>buprenorphine</td>
<td>8</td>
<td>mg</td>
<td>O</td>
<td>N07BC01</td>
</tr>
<tr>
<td>cilnidipine</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>C08CA14</td>
</tr>
<tr>
<td>darbepoetin alfa</td>
<td>4.5</td>
<td>mcg</td>
<td>P</td>
<td>B03XA02</td>
</tr>
<tr>
<td>desloratadine</td>
<td>5</td>
<td>mg</td>
<td>O</td>
<td>R06AX27</td>
</tr>
<tr>
<td>itraconazole</td>
<td>0.2</td>
<td>g</td>
<td>P</td>
<td>J02AC02</td>
</tr>
<tr>
<td>levocetirizine</td>
<td>5</td>
<td>mg</td>
<td>O</td>
<td>R06AE08</td>
</tr>
<tr>
<td>mifepristone</td>
<td>0.6</td>
<td>g</td>
<td>O</td>
<td>G03XB01</td>
</tr>
<tr>
<td>mycofenolic acid</td>
<td>2</td>
<td>g</td>
<td>P</td>
<td>L04AA06</td>
</tr>
<tr>
<td>nimesulide</td>
<td>0.2</td>
<td>g</td>
<td>O</td>
<td>M01AX17</td>
</tr>
<tr>
<td>peginterferon alfa-2b</td>
<td>7.5</td>
<td>mcg</td>
<td>P</td>
<td>L03AB10</td>
</tr>
<tr>
<td>propacetamol</td>
<td>6</td>
<td>g</td>
<td>P</td>
<td>N02BE05</td>
</tr>
<tr>
<td>talinolol</td>
<td>0.1</td>
<td>g</td>
<td>O</td>
<td>C07AB13</td>
</tr>
<tr>
<td>tobramycin</td>
<td>0.3</td>
<td>g</td>
<td>Inhal. sol.</td>
<td>J01GB01</td>
</tr>
<tr>
<td>zinc acetate, basic</td>
<td>0.15</td>
<td>g</td>
<td>O</td>
<td>A16AX05</td>
</tr>
</tbody>
</table>

**DDD changes:**

*Previous:* erythropoietin  
*New:* erythropoietin  
*Previous:* risedronic acid  
*New:* risedronic acid

176
ATC/DDD Classification (temporary)

The following temporary anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 21 October 2001. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, e-mail: whocc@nmd.no. If no objections are received, the new ATC codes and DDDs will be considered final and will be included in the January 2003 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

<table>
<thead>
<tr>
<th>ATC level</th>
<th>INN/common name</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>New ATC level codes (other than 5th levels):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other antihypertensives</td>
<td></td>
<td>C02KX</td>
</tr>
<tr>
<td>New ATC 5th level codes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aminolevulinic acid</td>
<td>L01XD04</td>
<td></td>
</tr>
<tr>
<td>apomorphine</td>
<td>G04BE07</td>
<td></td>
</tr>
<tr>
<td>bosentan</td>
<td>C02KX01</td>
<td></td>
</tr>
<tr>
<td>butenafine</td>
<td>D01AE23</td>
<td></td>
</tr>
<tr>
<td>calcipotriol, combinations</td>
<td>D05AX52</td>
<td></td>
</tr>
<tr>
<td>choriogonadotropin alfa</td>
<td>G03GA08</td>
<td></td>
</tr>
<tr>
<td>delapril and calcium channel blockers</td>
<td>C09BB12</td>
<td></td>
</tr>
<tr>
<td>dutasteride</td>
<td>G04CB02</td>
<td></td>
</tr>
<tr>
<td>eletriptan</td>
<td>N02CC06</td>
<td></td>
</tr>
<tr>
<td>famotidine, combinations</td>
<td>A02BA53</td>
<td></td>
</tr>
<tr>
<td>ferric sodium gluconate complex</td>
<td>B03AC07</td>
<td></td>
</tr>
<tr>
<td>fondaparinux sodium</td>
<td>B01AX05</td>
<td></td>
</tr>
<tr>
<td>gepirone</td>
<td>N06AX19</td>
<td></td>
</tr>
<tr>
<td>lafutidine</td>
<td>A02BA08</td>
<td></td>
</tr>
<tr>
<td>meningococcus C, purified polysaccharides antigen conjugated</td>
<td>J07AH07</td>
<td></td>
</tr>
<tr>
<td>miglustat</td>
<td>A16AX06</td>
<td></td>
</tr>
<tr>
<td>pegfilgrastim</td>
<td>L03AA13</td>
<td></td>
</tr>
<tr>
<td>seratrodast</td>
<td>R03DX06</td>
<td></td>
</tr>
<tr>
<td>simvastatin, combination packages</td>
<td>C10AA51</td>
<td></td>
</tr>
<tr>
<td>sulphur hexafluoride</td>
<td>V08DA05</td>
<td></td>
</tr>
<tr>
<td>tadalafil</td>
<td>G04BE08</td>
<td></td>
</tr>
<tr>
<td>tenecteplase</td>
<td>B01AD11</td>
<td></td>
</tr>
<tr>
<td>teriparatide</td>
<td>H05AA02</td>
<td></td>
</tr>
<tr>
<td>voriconazole</td>
<td>J02AC03</td>
<td></td>
</tr>
<tr>
<td>xaliproden</td>
<td>N07XX03</td>
<td></td>
</tr>
</tbody>
</table>
### ATC level

<table>
<thead>
<tr>
<th>ATC level</th>
<th>INN/common name</th>
<th>ATC code</th>
</tr>
</thead>
</table>

### ATC name changes:

**Previous:** parathyroid hormones

**New:** parathyroid hormones and analogues

### New DDDs:

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>DDD</th>
<th>Unit</th>
<th>Route of Administration</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>agalsidase alfa</td>
<td>1</td>
<td>mg</td>
<td>P</td>
<td>A16AB03</td>
</tr>
<tr>
<td>agalsidase beta</td>
<td>5</td>
<td>mg</td>
<td>P</td>
<td>A16AB04</td>
</tr>
<tr>
<td>amisulpride</td>
<td>0.1</td>
<td>g</td>
<td>O</td>
<td>N05AL05</td>
</tr>
<tr>
<td>amrenavir</td>
<td>2.4</td>
<td>g</td>
<td>O</td>
<td>J05AE05</td>
</tr>
<tr>
<td>apomorphine*</td>
<td>2</td>
<td>mg</td>
<td>SL</td>
<td>G04BE07</td>
</tr>
<tr>
<td>ascorbic acid</td>
<td>0.25</td>
<td>g</td>
<td>V</td>
<td>G01AD03</td>
</tr>
<tr>
<td>baclofen</td>
<td>0.55</td>
<td>mg</td>
<td>P</td>
<td>M03BX01</td>
</tr>
<tr>
<td>bisoxatin</td>
<td>0.12</td>
<td>g</td>
<td>O</td>
<td>A06AB09</td>
</tr>
<tr>
<td>diosmectite</td>
<td>9</td>
<td>g</td>
<td>O</td>
<td>A07BC05</td>
</tr>
<tr>
<td>eletriptan*</td>
<td>40</td>
<td>mg</td>
<td>O</td>
<td>N02CC06</td>
</tr>
<tr>
<td>estradiol</td>
<td>0.3</td>
<td>mg</td>
<td>N</td>
<td>G03CA03</td>
</tr>
<tr>
<td>lafutidine*</td>
<td>20</td>
<td>mg</td>
<td>O</td>
<td>A02BA08</td>
</tr>
<tr>
<td>levosimendan</td>
<td>11</td>
<td>mg</td>
<td>P</td>
<td>C01CX08</td>
</tr>
<tr>
<td>linezolid</td>
<td>1.2</td>
<td>g</td>
<td>O, P</td>
<td>J01XX08</td>
</tr>
<tr>
<td>lopinavir</td>
<td>8</td>
<td>g</td>
<td>O</td>
<td>J05AE06</td>
</tr>
<tr>
<td>lornoxicam</td>
<td>12</td>
<td>mg</td>
<td>P, R</td>
<td>M01AC05</td>
</tr>
<tr>
<td>lutropin alfa</td>
<td>75</td>
<td>U</td>
<td>P</td>
<td>G03GA07</td>
</tr>
<tr>
<td>naltrexone</td>
<td>50</td>
<td>mg</td>
<td>O</td>
<td>N07BB04</td>
</tr>
<tr>
<td>nateglinide</td>
<td>0.36</td>
<td>g</td>
<td>O</td>
<td>A10BX03</td>
</tr>
<tr>
<td>rasburicase</td>
<td>14</td>
<td>mg</td>
<td>P</td>
<td>V03AF07</td>
</tr>
<tr>
<td>rupatadine</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>R06AX28</td>
</tr>
<tr>
<td>sibutramine</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>A08AA10</td>
</tr>
<tr>
<td>sirolimus</td>
<td>6</td>
<td>mg</td>
<td>O</td>
<td>L04AA10</td>
</tr>
<tr>
<td>sodium selenite*</td>
<td>0.2</td>
<td>mg</td>
<td>O, P</td>
<td>A12CE02</td>
</tr>
<tr>
<td>terlipressin</td>
<td>12</td>
<td>mg</td>
<td>P</td>
<td>H01BA04</td>
</tr>
<tr>
<td>unoprostone</td>
<td>0.2</td>
<td>ml</td>
<td>N</td>
<td>S01EX04</td>
</tr>
</tbody>
</table>

### DDD changes:

**Previous:** budesonide 0.3 mg N

**New:** budesonide 0.2 mg N

* Temporary ATC code
Internet purchase of pharmaceuticals: a review of regulatory experience*

Countries vary considerably with regard to regulation of medicines sold over the Internet. Because of the cross-border nature of the Internet, regulations at international level should be favoured whenever possible particularly if these are seen to enhance harmonization of drug legislation. Notwithstanding this trend to globalization, there is always a risk of over regulation — and regulations which are too aggressive or restrictive will only deter innovative Internet pharmacy practices. In this environment, regulation can be seen as a powerful and positive tool to enable practitioners to engage in professional responsibilities towards patients by improving outcomes.

The Internet pharmacy can enhance and enable the practice of pharmaceutical care. Routine questions about medication can be answered by online pharmacists using e-mail or other electronic real-time video connections. Knowledge of a patient’s diagnosis, results of laboratory tests, and established drug monitoring parameters, largely unavailable to pharmacists at present, could be made accessible through the Internet. The vision of an e-enhanced pharmacy within the health care system is soon to become a reality.

The status of e-commerce of pharmaceuticals

In 2000, a survey was carried out to determine whether differences in the provision of pharmacy services exist among different types of US-based Internet pharmacies. This involved 5 chain pharmacy extensions, 6 mail order pharmacies, 14 online pharmacies and 8 independent pharmacy extensions allowing patients to purchase prescription medications online. There was significant variation among the four types of pharmacies. Patients were required to provide their own prescription at 88% of the sites. However several sites — particularly online pharmacies — either allowed the patient to obtain the prescription from the site’s online physician or made provisions for contacting the patient’s physician directly (1).

According to the data obtained, the most interesting finding was the variation in privacy and confidentiality policies. Chain pharmacy extensions were the most sensitive to this issue: such sites alerted users to their privacy policies during the ordering process and VIPPS-certified sites were more likely to do this. There was also a significant variation in availability of drug information — for example, only eight sites (24%) provided an electronic newsletter for patients but more than two-thirds provided a toll-free number for contacting a health care professional (1).

A study carried out in 1999 tested 46 websites selling prescription pharmaceuticals over the Internet. Thirty-seven sites (33 based in the USA and 4 based outside the United States) required a prescription from a personal physician or through an Internet physician consultation. Nine sites based outside of the United States did not require a prescription or physician consultation. The median cost of an Internet physician visit was US$ 70, which was considered to be 15% higher than the general practice visit locally. Median price per pill of two most commonly offered medications (sildenafil and finasteride) was 10% higher on the Internet (before shipping charges) than at local pharmacies in Philadelphia, USA (2).

A further study (3), used search engines (Altavista, HotBot, and WebCrawler) and identified 86 sites that offered to deliver sildenafil directly to consum-

* Compiled and commented by Harri Ovaskainen, Director for Pharmaceutical Affairs, Finnish Pharmacists’ Association, Helsinki, Finland
ers without a visit to a physician. In the 10-day interval between identification and data collection, nine sites operating within the United States ceased to exist. Forty-two (55%) of the 77 remaining sites required consumers to undergo an online medical evaluation, consisting of a questionnaire. Four sites (5%) offered, but did not require, such an evaluation and 31 sites (40%) did not offer such an evaluation. The average cost of an online evaluation was US$ 64 (IMF exchange rates were used to convert costs into dollars) and was separate from the cost of the drug. The average cost of a 50-mg tablet of sildenafil was US$ 12.60 (range: $5 to $40), and that of 100-mg tablet was US$ 13.50. Shipping and handling charges (range: $5 to $48) were added by 26 sites (34%) and all sites accepted credit-card payment for all costs.

The content and design of the questionnaire differed among the 46 sites (60%) that offered a questionnaire to their customers. Thirty-four of the sites required information about the use of nitrates before the respondent could submit the questionnaire, and 10 merely requested such information. Forty sites included questions about whether the respondent had been given a diagnosis and 33 of these sites required this information. On the other hand, at 52 websites (68%), consumers were required to consent to release the companies from any liability, and at 12 sites consumers were required to waive their need for physical examination (3).

To assure patient safety and avoid liability, many on-line pharmacy sites reject an order if a buyer’s questionnaire suggests that the drug may be medically inappropriate. However, on many sites, the process of analysing the questionnaire appears to be quite haphazard. For example, a newspaper reporter in Seattle contacted an Internet site, claimed normal weight, but was still able to order a prescription weight loss drug. Equally, a TV reporter ordered and got sildenafil for her 6-month-old son, using his actual height, weight, and birth date. Another investigator received the same drug after giving vital data for his cat. Though there are sites that do cull through questionnaires and reject inappropriate buyers, these systems remain ripe for abuse (4).

Two people working at the Austrian Health Institute (Österreichisches Bundesinstitut für Gesundheitswesen, ÖBIG) spent 6 months ordering 27 different prescription drugs through 20 online pharmacies. The results were not promising. One-third of all medicines ordered and paid for by credit card did not even arrive. Those that did, arrived with delays of up to 73 days only after several recalls. Even the prices were higher than in regular pharmacies — partly because of online consultation charges and shipping and handling fees. When delivered, the pills were never adequately packed in terms of mechanical and thermal protection. There were also deficiencies in the inclusion of information leaflets and in selling medications for incorrect indications (5).

A Swiss consultancy firm carried out a study of Internet purchase of prescription-only medicines or medicines not officially licensed in Switzerland. The study involved ordering, a total of 20 medicines from 9 different suppliers over the Internet. Seventeen medicines were delivered by mail within six weeks. They were sent in envelopes up to 8 cm thick, unopened and without having been inspected by customs. Five of the 17 medicines had been damaged during transport, leaving individual capsules or tablets open and unprotected in the envelope. Only two medicines were not supplied on the grounds that the person ordering them had not provided a doctor’s prescription. One medicine was not delivered for six weeks (6).

When products were analysed by the Swiss regulatory authority, the Intercantonal Medicines Bureau, they showed shortcomings in quality and quantitative composition. The products had excessive abrasion (brittleness), inadequate active ingredient content, unidentifiable impurities and misleading descriptions. In one case, the active ingredient was not exactly as declared, while another product contained the D-isomer instead of the L-isomer. No more than six of the medicines delivered contained a package insert, of which only one was in German. All other patient information leaflets were in English, Dutch, French, Italian or Spanish (6).

WHO questionnaire on the Internet and international regulatory control
To gain more information concerning the promotion and sale of medicines via the Internet, WHO distributed a questionnaire, in March 2000, to regulatory authorities controlling the sale and promotion of pharmaceuticals in each WHO Member State. The total number of replies was 58, representing just over one-third of Member States. Geographical distribution of these answers was Africa 8, America 6, Asia 26 and Europe 18.
Upon evaluation, it was evident that countries vary substantially in their regulations on the sale and promotion of medicines via the Internet. The outcome of the survey may not be statistically representative, but it does give a useful overview.

According to responses to the questionnaire, Denmark, Japan, Malaysia, Netherlands, New Zealand, Sweden, Switzerland, United Kingdom and United States of America have specific or general regulations on promotion and sale of medicines via the Internet. In some countries like Denmark, New Zealand and Sweden, the same general regulations on medicines apply to Internet sale, distribution and advertising as apply to usual commercial activity. In Israel and South Africa, regulation was planned and in Vanuatu legislation was under development.

Inspection of on-line pharmacies has so far only been carried out by the US Food and Drug Administration, although the number of inspections was not disclosed. The type of action taken for non-compliant premises was: convictions 12, arrests 28, warning letters 23, letters to foreign sellers 13, and import alerts 3.

National sanctions for patients importing medicines without a marketing authorization
Countries have different positions concerning patients importing pharmaceutical products which do not have marketing authorization in their country (excluding substances under international control). In some countries, such as the Czech Republic, this situation is not covered by law. More often, patients are free to import small quantities of medicines without a marketing authorization if these are for their personal use and/or their household. Countries that fall in this category are Bahrain, Brunei, Cyprus, Denmark, Estonia, Fiji Islands, Germany, Hungary, Japan, Malaysia, Mexico, Myanmar, Netherlands, Oman, Senegal, Spain, Sweden, Switzerland, United Kingdom, USA, Vanuatu, Venezuela. However, there may be some restrictions, for example, that the product should be prescribed by a physician in Brazil, India, Israel, Maldives and Philippines, while permission is required to import for personal use in India, Iran, Jordan, Lithuania, New Zealand, Singapore, Slovak Republic, Zimbabwe.

Many countries such as Antigua and Barbuda, Bangladesh (for large quantities), Hong Kong, Indonesia, Latvia, Mauritius, Mongolia, Nigeria, Samoa, South Africa, and Vietnam, reported sanctions for importing products without a marketing authorization. The minimum penalty varied between a fine or a fine and/or imprisonment up to seven years (Indonesia).

Companies/individuals engaging in commerce of pharmaceuticals without being licensed
This question seeks to determine if there are loopholes in legislation where companies/individuals can either import or wholesale pharmaceuticals without being licensed to do so. A country where export of pharmaceuticals is poorly controlled allows criminals to establish rogue Internet sites and operate with ease. Bangladesh, India, Jordan, Micronesia, Tonga and United Arab Emirates did not report on sanctions concerning this type of act. In most other countries, this is a criminal act subject to prosecution leading to either a fine and/or imprisonment. The seizure of stock and some other type of regulatory action can also exist. In some countries such as Estonia and the Slovak Republic, sanctions can vary depending on whether the offender is a physical or legal entity.

Companies/individuals involved in the retail and sale of prescription drugs without a valid prescription
This question indicates potential countries which either do not have strong control mechanisms for classifying prescription and OTC-medicines separately, or countries which have a loophole in their legislation. Countries not having sanctions for companies/individuals carrying out illegal retail selling of prescription medicines were Bangladesh, Jordan, Nigeria, Oman, Tonga and United Arab Emirates. The countries which accept that they do have difficulties in controlling this or have a culture of expanded self-medication are Brazil, Brunei, Malaysia and Myanmar. Sanctions for selling prescription drugs without valid prescriptions seem to consist of either a monetary fine or imprisonment. For licensed pharmacies or licensed practitioners, sanctions can include suspension or revocation of licensure.

In the perspective of Internet sales of pharmaceuticals, New Zealand identified a loophole in its legislation allowing online pharmacies to sell prescription drugs overseas without a valid prescription. This was challenged in court and tighter regulations were introduced in November 2000. These regulations now prohibit sales of prescription medicines to overseas consumers who do not have a prescription from a New Zealand authorized prescriber. The Medical Council of New Zealand has issued strict guidelines for doctors prescribing medicines over
Companies/individuals exporting pharmaceuticals without enquiring whether the products have a marketing authorization in the importing country or whether the importing company/individual is authorized.

This question provides information on potential sources of pharmaceuticals for online ‘rogue’ sites. It can give hints as to how the illegal Internet sellers can import their products — whether licensed or unlicensed in the importing country — without breaking the laws in the exporting country. The countries that did not have sanctions for exporting pharmaceuticals to an unauthorized importer and/or without enquiring from the importer before exporting whether the products have a marketing authorization in the importing country were Antigua and Barbuda, Bangladesh, Brazil, Czech Republic, Fiji (except substances under international control), Iceland, India, Indonesia, Israel, Japan, Jordan, Hungary, Maldives, Netherlands, Nigeria, Oman, Philippines, Singapore (except substances under international control), South Africa, Sweden, Switzerland, Tonga, United Arab Emirates, Vietnam and Zimbabwe.

Some countries, such as the UK have declared that the only control is the WHO Certification Scheme. However, New Zealand replied that there was no law ordering that WHO Certification must be obtained. Many countries (for example Hungary) stressed that at the moment it is up to the importing country to punish illegal actors. Most countries have enacted legislation that companies/individuals must be licensed in the exporting country to be able to start exporting in general.

Countries having export regulations for unapproved products were Belgium, Estonia, Latvia, Micronesia, Mongolia and the USA. The USA answered that for approved products, licensed wholesalers and registered distributors were responsible for assuring compliance with foreign laws. According to export law of 1996, unapproved products may be shipped by a US manufacturer either under an IND for a clinical study or to 25 countries (Europe, Japan, Canada, etc.) without FDA prior approval.

Some specific cases concerning pharmaceuticals and the Internet

In this section some countries are looked at more closely. The section begins with a short description of the policies in the European Union and three examples (Denmark, Germany and UK) of different approaches in EU member countries. The other countries that are introduced are Japan, New Zealand and USA.

The European Union

In December 1999, the European Commission launched the eEurope initiative. The goal of this initiative was to accelerate Europe’s transition to an “information” society. As requested by the Lisbon Summit in March 2000, the Commission prepared an eEurope Action Plan (7). The eEurope 2002 Action Plan was developed as a road map to where Europe should be by 2002 if it wanted to engage with competitors and meet the challenges of the new economy. The plan has three major topics: a cheaper, faster, and more secure Internet; stimulating use of the Internet, including e-commerce; and investing in people and skills (8).

In the European Union (EU), member countries have sovereignty over healthcare and, as a result, they can decide how they will organize the supply of medicines to the general public. The European Directives recognize two basic categories: prescription and non-prescription medicines. Depending on the category and the particular member country, different regulations of advertising and sale apply. Moreover, the legal status of some medicines differs between one member country and another.

In 1998, a legal consultant firm prepared a report and study for the Commission on the “Impact of electronic commerce on the European pharmaceutical sector”. A part of this study was a questionnaire which was sent to approximately 180 organizations across Europe with an interest in electronic commerce of pharmaceuticals. The survey indicated that pharmacist organizations were strongly opposed to e-commerce because of the possible threats to the patients’ health. Wholesalers, however, showed little interest in the subject and manufacturers were largely in favour of e-commerce with expectations that on-line sale of pharmaceuticals to consumers would become considerable. Regulators views were largely determined by their attitudes to regulation and free-market in general, so that regulators followed either a pro-free-market or pro-regulation line in their answers (9).

Self-prescription was difficult to argue, because some medicines are regarded as OTC-drugs in some EU countries and as prescription-only medicines in others. This was not regarded as a clear
option since health is at risk through purchase and use of prescription medicines without the required medical diagnosis, oversight and follow-up. In this context, it is important to note that the Internet might be misused for this purpose and that the existing heterogeneity among different member countries on the prescription-only status of some medicines could potentially influence this situation. Consumers may purchase a medicine as non-prescription in a member state whereas they need a medical prescription for it in another member state (10).

In some EU member countries (for example, Denmark and UK) national regulations permit community pharmacies to provide services on-line. According to the EU Directive on electronic commerce (2000/31/EEC) information on the Internet pharmacy site should meet the following requirements:

• Name of the pharmacy providing the service.

• The geographic addresses at which the pharmacy is established and its details (telephone and fax numbers) including e-mail address which allows rapid communication in a direct and effective manner.

• Professional title of the pharmacist responsible and country where granted.

• Professional body with which the pharmacist responsible is registered and the relevant supervisory authority (where applicable).

• Reference to the applicable professional rules in the country of establishment and means to access them.

A European Commission working group on information, advertising and e-commerce for medicinal products was set up in 2000.

Germany
In Germany, there are no regulations concerning the promotion and sale of medicines via the Internet. However, the Dutch e-pharmacy DocMorris operates a service for mailing of medicines to Germany. As a result of this practice, the regional civil court in Frankfurt-am-Main has submitted three questions concerning cross-border e-pharmacy to the Court of Justice of the European Communities (ECJ). The first question is whether national bans on cross-border commercial shipment of individually ordered, pharmacy-only medicines contravene the free movement of goods provisions of Article 28 of the EC Treaty or is such ban a measure equivalent to a restriction of trade (12).

The second question relates to advertising through distance selling of pharmaceuticals. The Frankfurt court asks whether the Internet presentation of pharmacy services, or parts of this presentation, should not be considered as promotion of human pharmaceuticals under the meaning of the pharmaceutical advertising Directive (92/28/EEC), in order to give practical expression to society's need for information on the provision of services.

The third question is whether parts of an Internet presentation of a pharmacy infringe the rules on medicines advertising. Articles 28 and 30, nonetheless, require that cross-border trade developed with the aid of this presentation be treated as legal in order that the principle of free movement of goods is given a more practical expression.

United Kingdom
The first online pharmacy in the UK — Pharmacy2U — was launched in November 1999. As a consequence, the Royal Pharmaceutical Society of Great Britain has issued guidance on the electronic commerce of pharmaceuticals (13) and the UK government has stated its support for online pharmacies (14). The UK Government's view is that if proper safeguards and professional standards are in place, there is no reason in principle why medicines should not be sold or dispensed electronically, or by other forms of distance sale and supply, like mail order or home delivery. At the moment online pharmacy services are offered to people for purchasing of OTC medicines and dispensing of private prescriptions. The UK Government believes that this choice should also be available to people with National Health Service prescriptions and will be bringing this service to cover routine electronic transmission of prescriptions by 2004.
Japan
Under the Japanese Pharmaceutical Affairs Law, pharmaceuticals should be sold face-to-face by a pharmacist or under his/her supervision. However, under certain conditions and for a limited scope of pharmaceuticals, direct mail and Internet sale is permitted. These conditions are:

1) The website must belong to a registered pharmacy or first-class drug seller.

2) Information on pharmaceuticals should be provided independently of that on other goods.

3) Name, address, licence number and date, owner and/or managing pharmacist of the pharmacy or first-class drug seller should be provided.

4) Dosage form, name and amount of active ingredients, indication, number of tablets per package, precautions, price and the name of manufacturer or importer should be provided.

5) General advice such as “Use this pharmaceutical product after carefully reading precautions” should be provided.

6) The telephone number for consultation should be shown.

7) A sufficient number of telephones and personnel should be available for callers.

8) Pharmaceuticals should not be mixed with other goods during delivery.

9) Pharmaceuticals should be provided in a solid container, with stable ingredients, few adverse drug reactions and their scope is uncomplicated, for examépe, antihemorrhoidal (except those containing steroids), dental analgesics and gastrointestinal agents (except gastrointestinal analgesics and antispasmodics).

New Zealand
New Zealand regulations prohibit sales of prescription medicines to individuals overseas who do not have a prescription from a New Zealand authorized prescriber. The requirement to have a New Zealand based prescription will restrict the ability of overseas consumers to purchase medicines pharmacies (15). Since November 2000, there has also been an Internet pharmacy accreditation system organized by the Pharmaceutical Society of New Zealand. The programme was introduced to officially recognize pharmacy sites that meet the prescribed professional standards for operating on the Internet. To be accredited, a pharmacy must comply with the ethical and legislative requirements and quality standards of a registered pharmacy. In addition, Internet sites displaying the accreditation seal must demonstrate compliance with patient rights to privacy and confidentiality, compliance with codes and legislative requirements for the advertising of medicines and the provision of factual and understandable information about all medicines advertised. The site must also provide the opportunity for meaningful consultation between patient and pharmacist. More information on this New Zealand accreditation system can be found at http://www.psnz.org.nz/

United States of America
The USA has a long history of mail-order pharmacies and many of them have extended their services to the Internet. The International Pharmaceutical Federation (FIP) Task Force Group on Internet pharmacies noted that the on-line pharmacies have come to resemble mail-order pharmacies. The Internet is a potentially interesting and interactive channel for customers, (16). In parallel to the true Internet pharmacies, many chain pharmacies have developed a cyberspace extension of brick-and-mortar stores, sometimes through alliances with existing online pharmacies (17). Other independent pharmacies have entered the Internet, as they believe it combines the convenience of the Internet with the trust associated with local pharmacists (18).

In July 1999, the FDA adopted, and has since implemented, an Internet Drug Sales Action Plan to expand and improve its activities in addressing the unlawful sale of drugs over the Internet. This was followed in December 1999, by proposals to protect US consumers when buying prescription drugs from online ‘rogue’ sites and gave the FDA authority to identify, investigate and prosecute web sites that do not comply with existing FDA and Pharmacy Board regulations (19).

Federal legislation has since been introduced to expand FDA authority over online pharmacies. The Internet Pharmacy Consumer Protection Act proposed amending the Food, Drug & Cosmetic Act (“FDCA”), which is under FDA implementation and enforcement authority. The bill prohibits online pharmacies from dispensing prescription drugs unless the website discloses information about who is selling the drugs. It also requires the identities of
the pharmacist and medical consultant, and where those persons are licensed to practice, to be disclosed (20). The FDA's testimony gives a good detailed explanation of what that Act aims to do. It will require:

- online pharmacies to be licensed in each State in which they operate or to which they deliver prescription drugs;
- compliance with all applicable Federal and State laws governing the practice of pharmacy, including those laws that require proper storage and handling of prescription drugs, proper record keeping, and other consumer protections;
- online pharmacies to post on their website a notice of their physical location, a list of States in which the online pharmacy is licensed to dispense prescription drugs and a list of applicable license numbers, the name, degree, and license of the pharmacist in charge; a telephone number for contacting a licensed pharmacist associated with the website, and a statement that the online pharmacy shall dispense prescription drugs only upon a valid prescription by a licensed practitioner (21).

In 2001, the FDA was provided with a budget of US$ 55 million to police the Internet. According to the Director of Pharmacy Affairs in the FDA, priorities are preventing unapproved new drugs from entering the US, dealing with health fraud: where patients have been deceived in some way, and preventing the sale of drugs without a valid prescription (19). The FDA has issued “cyber letters” (letters sent electronically via the Internet operators of foreign-based Internet sites that offer to sell online prescription drugs to US citizens without a valid — or in some cases without any — prescription (22).

Conclusions
Online pharmacies should be licensed and operated under the same regulatory system as traditional pharmacies. However, many countries still need to develop their legislation and guarantee the implementation of regulations which should also cover pharmacy inspections, including those of drug preparation and dispensing facilities and of controlled substance records (20).

Electronic prescribing is a technological prerequisite for effective e-commerce of prescription pharmaceuticals. However, regulations should allow only the dispensing of prescriptions that are valid in the country and/or state where the online pharmacy is licensed. Regulations and guidelines should also be developed for online prescribing so that the doctors will not prescribe medicines over the Internet for patients they have never met. Reimbursement, together with the issues of product categorization and pricing affect the development of e-commerce of pharmaceuticals. That is an especially important question when prescribing pharmaceuticals in countries that have reimbursement systems (9).

Until the e-commerce of pharmaceuticals has been satisfactorily regulated and organized, consumers should be warned of the risks of purchasing medicinal products via the Internet and especially the dangers of purchasing from illegal sites. They should also learn how to recognize nationally/locally accredited online pharmacies from illegal sites selling either prescription or OTC medicines.

References


22. FDA Talk Paper, T00-8 2 February 2000 http://www.fda.gov/bbs/topics/ANSWERS/ANS01001.html,


International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names (Rec. INN): List 46

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [Off. Rec. Wld Health Org., 1955, 60, 3 (Resolution EB15.R7); 1969, 173, 10 (Resolution EB43.R9)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy. Lists of Proposed (1–73) and Recommended (1–35) International Nonproprietary Names can be found in Cumulative List No. 9, 1996.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES (DCI Rec): Liste 46


Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS (DCI Rec.): Lista 46

De conformidad con lo que dispone el párrafo 7 del Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas [Act. Of. Mund. Salud, 1955, 60, 3 (Resolución EB15.R7); 1969, 173, 10 (Resolución EB43.R9)], se comunica por el presente anuncio que las denominaciones que a continuación se expresan han sido seleccionadas como Denominaciones Comunes Internacionales Recomendadas. La inclusión de una denominación en las listas de las Denominaciones Comunes Recomendadas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia. Las listas de Denominaciones Comunes Internacionales Propuestas (1–73) y Recomendadas (1–35) se encuentran reunidas en Cumulative List No. 9, 1996.
Latin, English, French, Spanish:

Recommended INN  Chemical name or description; Molecular formula; Graphic formula
DCI Recommandée  Nom chimique ou description; Formule brute; Formule développée
DCI Recomendada  Nombre químico o descripción; Fórmula empírica; Fórmula desarrollada

**abrineurinum**

abrineurin  
*N*-methyl-L-neurotrophic factor (human brain-derived) cyclic  
(13→80),(58→109),(68→111)-tris(disulfide), dimer

abrineurine  
dimère du (13→80),(58→109),(68→111)-tris(disulfure) cyclique du  
*L*-méthionylfacteur neurotrophique céphalique humain

abrineurina  
dimero del (13→80),(58→109),(68→111)-tris(disulfuro)cíclico del factor  
*N*-metionilneurotrófico (derivado de cerebro humano)

\[ \text{C}_{587}\text{H}_{947}\text{N}_{177}\text{O}_{177}\text{S}_{10} \text{(monomer)} \]

\[
\begin{align*}
\text{HSDPARRGEL} & \quad \text{SVCDISEWV} & \quad \text{TAADKTAVD} & \quad \text{MSGGTVTVLE} \\
\text{KVPVSKGQLK} & \quad \text{QYFYETKCNP} & \quad \text{MYTKEGRG} & \quad \text{IDKRHWNSQC} \\
\text{RTTQSYVRAL} & \quad \text{TMDSKKRIGW} & \quad \text{RFIDTSCV} & \quad \text{CLTIKRGR}
\end{align*}
\]

**acidum carglumicum**

carglumic acid  
*N*-carbamoyl-L-glutamic acid

acide carglumique  
acide (2S)-2-(carbamoylamino)pentanedioïque

ácido carglúmico  
ácido *N*-carbamoil-L-glutámico

\[ \text{C}_{6}\text{H}_{10}\text{N}_{2}\text{O}_{5} \]

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{H} & \quad \text{C} \\
\text{H} & \quad \text{N} \\
\text{O} & \quad \text{NH}_{2} \\
\text{HO}_{2}\text{C} & \quad \text{NH} & \quad \text{CO}_{2}\text{H}
\end{align*}
\]
**acidum lidadronicum**

lidadronic acid

[1-amino-3-(dimethylamino)propylidene]diphosphonic acid

acide lidadronique

acide [1-amino-3-(diméthylamino)propylidène]bisphosphonique

ácido lidadrónico

ácido[1-amino-3-(dimetilamino)propilideno]difosfónico

\[ \text{C}_4\text{H}_8\text{N}_2\text{O}_8\text{P}_2 \]

---

**agalsidasum alfa**

agalsidase alfa

human alpha-galactosidase isoenzyme A, isolated from human cell line, clone RAG 001, glycoform \( \alpha \)

agalsidase alfa

isoenzyme A de l’alpha-galactosidase humaine (dimère), glycoforme \( \alpha \)
produit par la lignée humaine RAG 001

agalsidasa alfa

isoenzima A de la alfa-galactosidasa humana glicosilada, aislada de cultivos de células humanas RAG 001, glicoforma \( \alpha \)

\[ \text{C}_{2500}\text{H}_{3007}\text{N}_{546}\text{O}_{972}\text{P}_{27} \]

(subunit protein moiety reduced)

LDNGLARTPT MGWLHWERFM CNLDCQEEPDP SCISEKLFME
MAELMVSEGW KDAGYEYLCC DDCWMAPQRD SEGRLOQAPQ
RFPHGIRQLA NYVHSHGKLKL GGYADVNGNKT CAGFPGSFGY
YDIDAQTFFAD WGVDLLKFDGG CYCDSLENLA DGYKHMLLAL
\( \hat{\text{N}} \)RTGRSIVYSS CEWPLYMWPFF QKPKNYTEIRQ YCNHRNFAD
IDDSWKSIKS ILDWTSFNQGE RIVDVAGPPG WNDPDMVLIG
NFGLSWNQQV TQMAMWAIMA APLFMSNDLR HISPQAKALL
QDKDVIAINQ DPLGKQGYQQL RQGNFEVWEE RPLSGLAWAV
AMINRQEIGG PRSYTIAVAS LGKGVACNPA CFITQLLPVK
RKLGFYEWTS RLRSHINPTG TVLLQLENMT QMSLKDNL

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

α-galactosidase (human clone λAG18 isoenzyme A subunit protein moiety reduced), glycoform β

agalsidase bêta

isoenzyme A de l’alpha-galactosidase humaine (dimère dont la partie protéique est codée par l’ADN de cellules λAG18 humaines) glycoforme β produit par culture de cellules ovariennes de hamster chinois (CHO)

agalsidasa beta

isoenzima A de la α-galactosidasa, fracción proteica reducida obtenida del clon humano λAG18, glicoforma β

C$_{580}$H$_{980}$N$_{298}$O$_{347}$S$_{20}$
(subunit protein moiety reduced)

LDNGLARTPT MGWLHERFM CNLDCQEPD SCISECFLME
MAELMVSEGW KDAYEYLCI DDCWMAPQRD SEGLQADPQ
RFPGRQGILA NYYSHKGLKL GIYADVGNKT CAGFPGSFGY
YDIDATFAD WGVDLKKFDD CYCDSLLENLA DGYKHMSLAL
NRTRGSIYVS CEWPLYMWPF QKPNYTEIRQ YCNHWRNFAD
IDDSWKSIS ILDWTSFNQE RIVDVAGPGG WNDPDMVLVG
NFGLSWQMQV TQMALWAIMA AFLMSNDLR HISPQAKALL
QDKVIAINOQ DLGKGYQYQL RQGDNFVWEW RPLSGLAVAV
AMINQEGIGG PRSYTIAVAS LGKGVACNPA CFITQLPGVK
RKLGFYWETS RLRSHINPTG TVLLQLENTM QMSLKDLL

alefaceptum

alefacept

1-92-antigen LFA-3 (human) fusion protein with human immunoglobulin G1 (hinge-C$_{2}$-C$_{3}$ γ1-chain), dimer

aléfacept

dimère de la protéine de fusion entre le 1-92-LFA-3 humain et la région charnière C$_{2}$-C$_{3}$ de la chaîne γ1 de l’immunoglobuline G1 humaine

alefacept

dímero de la proteína de fusión entre el 1-92-antígeno LFA-3 humano y la immunoglobulina G1 (cadena γ1 bisagra-C$_{2}$-C$_{3}$)

C$_{554}$H$_{902}$N$_{250}$O$_{296}$S$_{17}$

FSQQIYGVYV GNVTFHVPSN VPLKEVLWKQ KQDKVAELN
SEFRAFSSFK NRVYLDVSG SLTIYNTSS DEDEYEMESP
NITDTRNFLL YV DKHTCPP C PAPELLGGP SVFLFPKP
K P
D LTLMISRTPE VTCVVDVSH EDPEVKFNWV VDGVEHNAK
TKPREEQYN T YRVVSLTV LHQDWLNGKE YKCKVSNKAL
PAPIERTISK AKQPGPREPV YTLPPSRDEL TKQNQVSLCTL
VKGFYPSDIA VEWESNGQPE NNYYTTPVL DSDDGSFLYS
KLTVKSRW QGNVFSCWSM HEALHNHYTQ KSLSLSPGK
**alfatradiolum**  
alfatradiol | estra-1,3,5(10)-triene-3,17α-diol  
alfatradiol | estra-1,3,5(10)-triène-3,17α-diol  
alfatradiol | estra-1,3,5(10)-trieno-3,17α-diol  
C$_{25}$H$_{35}$O$_2$  

**aprepitatum**  
apreptant | 3-[[2R,3S]-3-((p-fluorophenyl)-2-[[((αR)-α-methyl-3,5-bis(trifluoromethyl)benzyl]oxy][morpholino[methyl]-Δ$^1$-1,2,4-triazolin-5-one  
aprépant | 5-[[2R,3S]-2-[(1R)-1-[3,5-bis(trifluorométhyl)phényl]éthoxy]-3-(4-fluorophényl)morpholin-4-yl[méthyl]-1,2-dihydro-3H-1,2,4-triazol-3-one  
apreptant | 5-[[2R,3S]-2-[(1R)-1-[3,5-bis(trifluorometil)fenil]etoxi]-3-(4-flurofenil)morfolin-4-il]metil]-1,2-dihidro-3H-1,2,4-triazol-3-ona  
C$_{21}$H$_{29}$F$_3$N$_4$O$_3$  

**atrasentanum**  
atrasantan | (2R,3R,4S)-1-[(dibutylcarbamoyl)methyl]-2-(p-methoxyphenyl)-4-[3,4-(methyleneoxy)phenyl]-3-pyrrolidinecarboxylic acid  
atrasantan | acide (2R,3R,4S)-4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoéthyl]-2-(4-méthoxyphényl)pyrrolidine-3-carboxylique  
atrasentán | ácido (2R,3R,4S)-1-[(dibutilcarbamoi)metil]-2-(p-metoxifenil)-4-[3,4-(metilenodoxi)fenil]-3-pirrolidinacarboxilico
aviscumenum
aviscumine
toxin ML-I (mistletoe lectin I) (*Viscum album*)

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

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

\[ C_{207}H_{399}N_{46}O_{27+S} \, (A) \]

\[ C_{207}H_{399}N_{46}O_{27+S} \, (B) \]

| MYERIRLRTVE | HQTTEGEYFR | FITLLRDYVS | SGFSNEIPL |
| LRIQSTIPVSD | AQRFVLVELT | NQGGSITAA | IDVTLNYVVA |
| YQAGDQSYFL | RDAPRGAETH | LFTGTRSSL | PFNGSYPDLE |
| RYAGHRDQIP | LGIDQLIQSV | TALRFPGGST | RTQARSILIL |
| IQMISEAARF | NPILWRARQY | INSGASFLPD | VYMLETSTSW |
| GQOSTQVQHS | TDGVFFNPIR | LAIPPNGFVT | LTNVRDVIAS |
| LAIMLVCGE |

| MDDVTCASE | PTVRIVGRNG | MCVDVRDDDF | RDGNQIQGLWP |
| SKSNNDPNQL | WTIKRDTGIR | SNSCSTTYG | YTAGVYVMIF |
| DCNTAVREAT | LWQIWNGTI | INPRSNLVA | ASSGIKGTTL |
| TVQTLTSLQ | QGWLAGNDA | PREVTIYGR | DLCMESNNGS |
| VMMVTCSSQ | KQRWALYGD | GSRIPKQNOQD | QCLTCGRDSV |
| STVINIVSCS | AGSSGQRWVF | TNEGAILNLK | NGLAMDVAQA |
| NPKLRRIIIY | PATGKPNQMWM | LPVP |
**balaglitzazonum**

balaglitzzone  
$(\pm)-5\{p\{(3,4\text{-dihydro}-3\text{-methyl}-4\text{-oxo-2-quinazolinyl} \text{methoxy}}\text{benzyl}\} \text{-2,4-thiazolidinedione}$

balaglitzzone  
$(5RS)-5\{4\{(3\text{-méthyl}-4\text{-oxo-3,4-dihydroquinazolin-2-yl) méthoxy} \text{benzyl}\} \text{thiazolidine-2,4-dione}$

balaglitzona  
$(\pm)-5\{p\{(3,4\text{-dihdro}-3\text{-metil}-4\text{-oxo-2-quinazolinil} \text{metoxi} \text{bencil}\} \text{-2,4-tiazolidinadiona}$

$C_{28}H_{27}N_{1}O_{5}S$

---

**bimosiamosum**

bimosiamose  
$[\text{hexane-1,6-diylbis[6'},(\alpha\text{-D-mannopyranosyloxy)biphenyl-3',3-diyl]]diacetic acid}$

bimosiamose  
$\text{acide [hexane-1,6-diylbis[6'},(\alpha\text{-D-mannopyranosyloxy)biphényle-3',3-diyl]]diacétique}$

bimosiamosa  
$\text{ácido [hexano-1,6-diilbis[6'},(\alpha\text{-D-manopiranosiloxi)bifenil-3',3-diil]]diacético}$

$C_{46}H_{32}O_{15}$
brostallicinum  
brostallicin  
4-(2-bromoacrylamido)-N''-(2-guanidinoethyl)-1,1',1'',1'''-tetramethyl-N,4':N',4''':N'',4''''-quater[pyrrole-2-carboxamide]

brostallicine  

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

\[ \text{C}_{50}\text{H}_{35}\text{BrN}_{12}\text{O}_5 \]

\[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{Br} \\
\text{O} \\
\text{O} \\
\text{H} \\
\text{H} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{C}_\text{H}_3 \\
\text{N} \\
\text{C}_\text{H}_3 \\
\text{N} \\
\text{O} \\
\end{array}
\]

dabigatranum  
dabigatran  
\( N-[[2-[(p-ami\text{dinoanilino})methyl]-1-methyl-5-benzimidazolyl]carbonyl]-N-2-pyridy\text{l}-\beta-\text{alanine} \)

dabigatran  
acide 3-[[2-[[4-(ami\text{noiminométhyl})phényl]amino]méthyll]-1-\text{méthyl}-1H-benzimidazol-5-yl]carbonyll[(pyridin-2-yl)amino]\text{propanoique}

dabigatrán  
\( N-[[2-[(p-ami\text{dinoanilino})metil]-1-metil-5-benzimidazolil]carbonil]-N-2-piridill-\beta-\text{alanina} \)

\[ \text{C}_{29}\text{H}_{27}\text{N}_7\text{O}_3 \]

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{N} \\
\text{H}_2\text{N} \\
\text{N} \\
\text{N} \\
\text{O} \\
\text{C}_\text{H}_3 \\
\text{O} \\
\text{CO}_2\text{H} \\
\text{N} \\
\text{N} \\
\text{H}_3\text{C} \\
\end{array}
\]
**dilomotecanum**

**dilomotecan**

(5R)-5-ethyl-9,10-difluoro-1,4,5,13-tetrahydro-5-hydroxy-3H,15H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione

**dilomotécan**

(5R)-5-éthyl-9,10-difluoro-5-hydroxy-1,4,5,13-tétrahydro-3H,15H-oxépino[3',4':6,7]indolizino[1,2-b]quinoléine-3,15-dione

**dilomotecán**

(5R)-5-etil-9,10-difluoro-1,4,5,13-tetrahidro-5-hidroxi-
3H,15H-oxepino[3',4':6,7]indolizino[1,2-b]quinolina-3,15-diona

\[
C_{27}H_{30}F_{2}N_{2}O_{4}
\]

---

**edotre tidum**

**edotretide**

\[
N-[[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-threonyl-
N'-(1R,2R)-2-hydroxy-1-{(hydroxymethyl)propyl}]-L-cysteamide cyclic (2→7)-disulfide
\]

**édotréotide**

(2→7)-disulfure cyclique du \[N-[[4,7,10-tris(carboxyméthyl)-1,4,7,10-
tétraazacyclodéc-1-yl]acétyl]-D-phénylalanyl-L-cystéinylique-L-tyrosyl-
D-trytophyll-L-lysyl-L-thréonyle-N'-(1R,2R)-2-hydroxy-
1-{(hydroxyméthyl)propyl}]-L-cystéaminide\]

**edotretida**

(2→7)-disulfuro cíclico de \[N-[[4,7,10-tris(carboximetil)-1,4,7,10-
tetraazaciclododec-1-il]acetil]-D-fenilalanil-L-cisteinil-L-tirosil-D-trytophil-L-lisil-
L-threoniil-N'-(1R,2R)-2-hidroxi-1-{hidroximetililpropil}]-L-cisteinamida

\[
C_{60}H_{59}N_{14}O_{14}S_{2}
\]
edronocainum
edronocaine  
$N,1$-dimethyl-$2'-(m$\text{-}$propoxyphenoxy)$diethylamine

édronocaine
$N$-méthyl-$N$-$[2-(3$\text{-}$propoxyphénoxy)$éthyl]$propan$-2$-amine

edronocaína
$N,1$-dimentil-$2'-(m$\text{-}$propoxifenoxi)$diethylamina

\[
C_{14}H_{22}NO_2
\]

\[
\begin{array}{c}
\text{CH}_3 \\
\text{O} \\
\text{H}_2\text{C} - \text{O} \\
\text{N} - \text{CH}_3
\end{array}
\]

eflucimibum
eflucimibe  
(S)$-2$-(dodecylthio)$-4'$-hydroxy$-2',3',5'$-trimethyl$-2$-phenylacetanilide

éflucimibe  
$(2S)$-$2$-(dodécylsulfanyl)$-N$-$[4$-$hydroxy$-2,3,5$-$triméthylphényl]$-
2$-phénylacétlamide

eflucimiba
(S)$-2$-(dodeciltio)$-4'$-hidroxi$-2',3',5'$-trimetil$-2$-fenilacetanilida

\[
C_{26}H_{38}NO_2S
\]

\[
\begin{array}{c}
\text{H}_2\text{C} \\
\text{S} \\
\text{H} \\
\text{N} - \text{CH}_3 \\
\text{O} \\
\text{CH}_3 \\
\text{OH} \\
\text{CH}_3 \\
\text{OH}
\end{array}
\]

eganoprostum
eganoprost  
methyl  $(Z)$-$7$-$[(1R,2R,3R)$-$2$-$[(1E,3S,7R)$-3,7$-dihydroxy$-1$-octeny]-
3$-hydroxy$-5$-oxocyclopentyl]$-5$-heptenoate

ganoprost  
$(Z)$-$7$-$[(1R,2R,3R)$-$2$-$[(1E,3S,7R)$-3,7$-dihydroxyoct$-1$-ényl]-3$-hydroxy$-
5$-oxocyclopentyl]$hept$-5$-énoate de méthyle

ganoprost  
$(Z)$-$7$-$[(1R,2R,3R)$-$2$-$[(1E,3S,7R)$-3,7$-dihidroxioc$-1$-enil]-3$-hidroxii-
5$-oxociclopentil]$hept$-5$-enoato de metilo

\[
C_{21}H_{34}O_6
\]

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{OH} \\
\text{H} \\
\text{OH} \\
\text{OCH}_3 \\
\text{OH}
\end{array}
\]
**emodepsidum**

emodepside  
\[\text{cyclo}[(R)-\text{lactoyl-}N\text{-methy}lL\text{-leucyl-(R)-3-(p-morpholinophenyl)}\text{lactoyl-}N\text{-methyl-L-leucyl-(R)-lactoyl-N-methyl-L-leucyl-(R)-3-(p-morpholinophenyl)}\text{lactoyl-N-methyl-L-leucyl}]\]

emédiapside  
\[\text{cyclo}[(R)-2\text{-hydroxypropanoyl-}(N\text{-methyl-L-leucyl})\text{-[(R)-3-[4-(morpholin-4-yl)phényl]}\text{-2-hydroxypropanoyl-}(N\text{-methyl-L-leucyl})\text{-[(R)-2-hydroxypropanoyl-}(N\text{-methyl-L-leucyl})\text{-[(R)-3-[4-(morpholin-4-yl)phényl]}\text{-2-hydroxypropanoyl-}(N\text{-methyl-L-leucyl})]}\]

emodepsida  

\[\text{C}_{60}\text{H}_{90}\text{N}_{10}\text{O}_{14}\]

**erlizumabum**

erlizumab  
immunoglobulin G1, anti-(human antigen CD18) (human-mouse monoclonal F\(\text{ab}’\), fragment γ1-chain), disulfide with human-mouse monoclonal light chain, dimer

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

erlizumab  
immunoglobulina G1, anti-(antígeno CD18 humano) fragmento F\(\text{ab}’\), (cadena γ1 del anticuerpo monoclonal humanizado de ratón), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal humanizado de ratón
**ertapenemum**

**ertapenem**

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

**ertapénem**


**ertapenem**


$$C_{22}H_{29}N_3O_S$$

![Structure of ertapenem](image)

---

**etiricoxibum**

**etiricoxib**

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

**étiricoxib**

5-chloro-6'-méthyl-3-[4-(méthylsulfonyl)phényl]-2,3'-bipyridyle

**etiricoxib**

5-cloro-6'-metil-3-[4-(métisulfonil)fenil]-2,3'-bipiridilo

$$C_{19}H_{20}ClN_2O_2S$$

![Structure of etiricoxib](image)
**eufauerasum**
eufauerase

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

eufausérase

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

eufaueresa

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

\[ C_{1172}H_{1794}N_{320}O_{38}S_{14} \]

AVENCVPVAP RNK

IVGGMEVTPH AYPWQVGLFI DDMYFCGGSI ISDEWVLTAH

CMDGAGFVEV VMGAHSIHDE TEATQVRATS TDFTHENWN

SFTLSNDLAL IKMPAPIEFN DVIQPVCLPT YTDASDFVG

ESVLTGKGK PSDSAFGIAE QLREVVDHTI TTADCOYYG

IVTDKILCID SEGGHGSCNG DSGPMPNYYT GGVQTRGVT

SFGSSGCET GYPDGYTRVT SYLDWIESNT GIAIDP

**farglitazarum**
farglitazar

\( N\text{-}(\text{o-Benzoylphényl})\text{-}O\text{-}[2\text{-}(\text{5-méthyl-2-phenyl-4-oxazolyl})\text{-}ethyl]\text{-}l\text{-}tyrosine \)

farglitazar

acide \((2S)\text{-}2\text{-}[2\text{-}(\text{benzoilphényl})\text{amino}]\text{-}3\text{-}[4\text{-}[2\text{-}(\text{5-méthyl-2-phényloxazol-4-yl})\text{éthoxy}phényl])\text{propanoique} \)

farglitazar

ácido \((2S)\text{-}2\text{-}[2\text{-}benzoi(fenil)]amino]3\text{-}[4\text{-}[2\text{-}(\text{5-metil-2-feniloxazol-4-il})\text{etoxi}fenil]propanoico \)

\[ C_{36}H_{30}N_2O_5 \]
fesoterodinum  
**fesoterodine**  
2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate

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

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

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

gemopatrilatum  
**gemopatrilat**  
(6S)-hexahydro-6-[(αS)-α-mercaptohydrocinnamido]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid

gémopatrilate  

gemopatrilat  

\[
C_{28}H_{33}NO_3
\]
imatinib

\[\alpha-(4\text{-methyl-1-piperazinyl})-3'\text{-[4-(3-pyridyl)-2-pyrimidinyl]amino}-p\text{-toluene-toluidide}\]

\[\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_2\]

\[\text{H-Gly-Ile-Val-Glu-Gln-Cys-Cys-Thr-Ser-Ile-Cys-Ser-Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys-Asn-OH}\]


insulinum glulisinum

insulin glulisine [3\text{\textsuperscript{a}}-L-lysine,29\text{\textsuperscript{a}}-L-glutamic acid]insulin (human)

insuline glulisine [3\text{\textsuperscript{a}}-L-lysine,29\text{\textsuperscript{a}}-L-acide glutamique]insuline humaine

insulina glulisina [3\text{\textsuperscript{a}}-L-lisina,29\text{\textsuperscript{a}}-L-acido glutámico]insulina humana

\[\text{C}_{285}\text{H}_{384}\text{N}_{76}\text{O}_{56}\]

lémalsomabum

lémalsomab immunoglobulin G1, anti-(human NCA-90 granulocyte cell antigen) (mouse monoclonal IMMU-MN3 γ1-chain), disulfide with mouse monoclonal IMMU-MN3 κ-chain, dimer

lémalsomab immunoglobuline G1, anti-(antigène cellulaire du granulocyte humain NCA-90) (chaîne γ1 de l’anticorps monoclonal de souris IMMU-MN3), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal de souris IMMU-MN3

lémalsomab immunoglobulina G1, anti-(antígeno celular del granulocito humano NCA-90) (cadena γ1 del anticuerpo monoclonal de ratón IMMU-MN3), dimero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón MMU-MN3
litomeglovirum
litomeglovir 2-[[4-[[5-(dimethylamino)-1-naphthyl]sulfonamido]phenyl]carbamoyl]-2-methylpropyl glycinate

litoméglôvir aminoacétate de 3-[[4-[[5-(diméthylamino)naphtalén-1-yl]sulfonyl]amino]phényl]amino]-2,2-diméthyl-3-oxopropylique

litomeglovir aminoacetato de 3-[[4-[[5-(dimetilamino)naftalen-1-il]sulfonil]amino]fenil]amino]-2,2-dimetil-3-oxopropilo

\[\text{C}_{25}\text{H}_{32}\text{N}_{3}\text{O}_{5}\text{S}\]

micafunginum
micafungin (4R,5R)-4,5-dihydroxy-N^2-[4-[4-(pentiloxy)phenyl]-3-isoaxolyl]benzoyl]-L-ornithyl-L-threonyl-trans-4-hydroxy-L-prolyl-(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfophenyl)]amino-L-threonyl-(3R)-3-hydroxy-L-glutaminyl-(3S,4S)-3-hydroxy-4-methyl-L-proline cyclic (6→1)-peptide

micafungine hydrogéno sulfaté de 5-[[1S,2S]-2-[[2R,6S,9S,11R,12R,14aS,15S,16S,20S, 23S,25aS]-20-[[1R]-3-amino-1-hydroxy-3-oxopropyl]-2,11,12,15-tétrahydropyrrolo[2,1-c:2,1'-c' ][1,4,7,10,13,16]hexaazacyclohexadecosé-23-yl]-1,2-dihydroxyéthyl]-2-hydroxyphényl

mozenavir

mozenavir \( (4R,5S,6S,7R)-1,3\text{-bis}(3\text{-aminobenzyl})-4,7\text{-dibenzylhexahydro-5,6-dihydroxy-2H-1,3-diazepin-2-one} \)

mozénavir \( (4R,5S,6S,7R)-1,3\text{-bis}(3\text{-aminobenzyl})-4,7\text{-dibenzyl-5,6-dihydroxyhexahydro-2H-1,3-diazépin-2-one} \)

mozenavir \( (4R,5S,6S,7R)-1,3\text{-bis}(3\text{-aminobenzil})-4,7\text{-dibenzil-5,6-dihidrohexahidro-2H-1,3-diazepin-2-ona} \)

\[ C_{56}H_{77}N_{22}O_{23}S \]
navuridinum
navuridine
3'-azido-2',3'-dideoxyuridine

navuridine
1-(3-azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)pyrimidine-2,4(1H,3H)-dione

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

C_{9}\text{H}_{11}\text{N}_{3}\text{O}_{4}

neramexanum
neramexane
1,3,3,5,5-pentamethylcyclohexylamine

néramexane
1,3,3,5,5-pentaméthylcyclohexanamine

neramexano
1,3,3,5,5-pentametilciclohexilamina

C_{11}\text{H}_{22}\text{N}

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

nolomirolo
bis(2-méthylpropanoate) de (6RS)-6-(méthylamino)-5,6,7,8-tétrahydronaphtalène-1,2-diyle

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

C_{9}\text{H}_{20}\text{NO}_{4}

and enantiomer
et énantiomère
y enantiómero
**omaciclovirum**

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

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

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

\[C_{14}H_{16}N_2O_3\]

---

**omalizumabum**

**omalizumab**

**omalizumab**
immunoglobuline G, anti-(région Fc de l’immunoglobuline E humaine) (chaîne \(\gamma\) de l’anticorps monoclonal de souris E25 clone pSVIE26 humanisé), dimère du disulfure avec la chaîne \(\kappa\) de l’anticorps monoclonal de souris E25 clone pSVIE26 humanisé

**omalizumab**
immunoglobulina G, anti-(región Fc de la inmunoglobulina E humana) (cadena \(\gamma\) del anticuerpo monoclonal humanizado de ratón E25 clon pSVIE26), dimero del disulfuro con la cadena \(\kappa\) del anticuerpo monoclonal humanizado de ratón E25 clon pSVIE26

---

**peginterferonum alfa-2a**

**peginterferon alfa-2a**
mono(\(N^2, N^6\)-dicarboxy-L-lysyl)interferon alfa-2a, diesters with polyethylene glycol monomethyl ether
The molecular mass of the pegylated part may be indicated in the name by adding a number, for example: peginterferon alfa-2a (40KD).

**peginterféron alfa-2a**
interféron alfa-2a dont une des lysines en position 31, 121, 131 ou 134 est acylée par le \(N^2, N^6\)-bis[méthylpoly(oxyéthylène)oxycarbonyl]-L-lysyl
La masse molaire de la partie polyéthyléneglycol peut être indiquée dans la DCl, par exemple: peginterféron alfa-2a (40KD).

**peginterferón alfa-2a**
diésteres del mono (\(N^2, N^6\)-dicarboxí- L-lisil) interferón \(\alpha\)-2a, con polietilenglicolmonometiléter
La masa molecular de la parte pegilada, si es necesario, puede indicarse en el nombre añadiendo un número, por ejemplo: peginterferón alfa-2a (40KD).
peginterferon alfa-2b

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

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

peginterféron alfa-2b

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

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

peginterferón alfa-2b

diésteres del monocarboxyinterferón alfa-2b con éter monometílico de polietilenglicol

La masa molecular de la parte pegilada, si es necesario, puede indicarse en el nombre añadiendo un número, por ejemplo: peginterferón alfa-2b (12KD).
pipendoxifenum

pipendoxifène

pipendoxifeno

2-((p-hydroxyphenyl)-3-methyl-1-[p-(2-piperidinoethoxy)benzyl]indol-5-ol

C_{39}H_{34}N_{2}O_{3}

pitrakinraum

pitrakinra

C_{91}H_{102}N_{10}O_{20}S_{9}

HKCDITLQEI IKTLSLTLTEQ KTLCTELTWT DIFAAKNTT
EKETFCRAAT VLRQFYSHHE KDTRCLGATA QQFHRHKQLI
RFLKRLDRNL WGLAGLNSCP VKEANQSTLE NFRLKLTIM
DEKDSKCSS
**pradofloxacínium**

**pradofloxacín**

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

**pradofloxacínací**

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

\[
C_{21}H_{25}FNO_3
\]

**reglitazarum**

**reglitazar**

\((4RS)\)-4-[[2-(5-metil-2-phenil-4-oxazolil)etoxi]benzil]-3,5-isoxazolidinedion

**réglitazar**

\((4RS)\)-4-[[2-(5-méthyl-2-phényloxazol-4-yl)éthoxy]benzil]isoxazolidine-3,5-dione

**reglitazar**

\((4RS)\)-4-[[2-(5-metíl-2-feníloxazol-4-il)etoxi]bencil]isoxazolidina-3,5-diona

\[
C_{25}H_{23}N_5O_5
\]

**rivoglitazonum**

**rivoglitazón**

\((\pm)\)-5-[[6-metoxi-1-metil-2-benzimidazolil]methoxi]benzil]-2,4-thiazolidinedion

**rivoglitazón**

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

**rivoglitazona**

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

\[
C_{25}H_{23}N_5O_5S
\]
### sabiporidum

**sabiporide**  
\( N\text{-carbamimidoyl-4-[4-(1H-pyrrol-2-ylcarbonyl)piperazin-1-yl]-3-(trifluoromethyl)benzamide} \)

**sabiporide**  
\( N\text{-carbamimidoyl-4-[4-(1H-pyrrol-2-ylcarbonyl)pipérazin-1-yl]-3-(trifluorométhyl)benzamide} \)

**sabiporida**  
\( N\text{-carbamimido-4-[4-(1H-pirrol-2-ilcarbonil)pipérazin-1-il]-3-(trifluorometil)benzamida} \)  
\( C_{18}H_{17}F_{2}N_{3}O_{2} \)

![Chemical Structure](image1.png)

### safinamidum

**safinamide**  
\( (\pm)-(S)\text{-2-[[p-[(m-fluorobenzyl)oxy]benzyl]arnino]propionamid} \)

**safinamide**  
\( (2S)\text{-2-[[4-(3-fluorobenzyloxy)benzyl]arnino]propanamid} \)

**safinamida**  
\( (\pm)-(S)\text{-2-[[p-[(m-fluorobencil)oxi]bencil]arnino]propionamid} \)  
\( C_{17}H_{16}F_{2}N_{2}O_{2} \)

![Chemical Structure](image2.png)

### sibenadetum

**sibenadet**  
\( 4\text{-hydroxy-7-[[2-[[3-[(2-phenylethoxy)propyl]sulfonyl]ethyl]arnino]ethyl]benzothiazol-2(3H)-one} \)

**sibénadet**  
\( 4\text{-hydroxy-7-[[2-[[3-[(2-phénylethoxy)propyl]sulfonyl]éthyl]arnino]éthyl]benzothiazol-2(3H)-one} \)

**sibenadet**  
\( 4\text{-hidroxi-7-[[2-[[3-[(2-feniletotox]propil]sulfonil]etil]arnino]etil]benzotiazol-2(3H)-ona} \)

\( C_{22}H_{28}N_{3}O_{3}S_{2} \)

![Chemical Structure](image3.png)
soblidotinum

**soblidotin**

\[N^2-(N,N\text{-dimethyl-L-valyl})-N'\text{-}[(1S,2R)-2\text{-}methoxy\text{-}4\text{-}[(2S)\text{-}2\text{-}[(1R,2R)\text{-}1\text{-}methoxy\text{-}2\text{-}methyl\text{-}3\text{-}oxo\text{-}3\text{-}[(2\text{-}phenylethyl)amino]propyl\text{-}1\text{-}pyrrolidinyl}\text{-}1\text{-}[(1S)\text{-}1\text{-}methylpropyl]\text{-}4\text{-}oxobutyrl]}\text{-}N'\text{-}methyl-L-valinamid}]

**soblidotine**

\[(2S)\text{-}2\text{-}[(2S)\text{-}2\text{-}(dimethylamino)\text{-}3\text{-}methylbutanoyl]amino\text{-}N\text{-}[(1S,2R)\text{-}2\text{-methoxy}4\text{-}[(2S)\text{-}2\text{-}[(1R,2R)\text{-}1\text{-methoxy}2\text{-}methyl3\text{-}oxo3\text{-}[(2\text{-}phenylethyl)amino]propyl]pyrrolidin1\text{-}yl\text{-}1\text{-}[(1S)\text{-}1\text{-methylpropyl}]\text{-}4\text{-oxobutyrl]}\text{-}N,3\text{-dimethylbutanamide}]

**soblidotina**

\[(2S)\text{-}2\text{-}[(2S)\text{-}2\text{-}(dimetilamino)\text{-}3\text{-metilbutanoil]amino\text{-}N\text{-}[(1S,2R)\text{-}2\text{-metoxi4\text{-}[(2S)\text{-}2\text{-}[(1R,2R)\text{-}1\text{-metoxi}2\text{-}metil3\text{-oxo3\text{-}[(2\text{-feniletil)amino]propil}pyrrolidin1\text{-}yl\text{-}1\text{-}[(1S)\text{-}1\text{-metilpropil}]\text{-}4\text{-oxobutil]}\text{-}N,3\text{-dimetilbutanamida}]

\[C_{30}H_{53}N_5O_6\]

---

**soneclosanum**

**soneclosan**

5-chloro-2-(p-chlorophenoxyl)phenol

**sonéclosan**

5-chloro-2-(4-chloroéphoxyl)phénol

**soneclosán**

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

\[C_{11}H_{12}ClO_2\]

---

**sumanirolum**

**sumanirole**

\[(R)\text{-}5,6\text{-dihydro}5\text{-}(methylamino)4H\text{-imidazo}[4,5,1-ij]quinolin2(1H)\text{-}one\]

**sumanirole**

\[(5R)\text{-}5\text{-}(méthylamino)5,6\text{-dihydro}4H\text{-imidazo}[4,5,1-ij]quinoléin2(1H)\text{-}one\]

**sumanirol**

\[(5R)\text{-}5\text{-}(metilamino)5,6\text{-dihidro}4H\text{-imidazo}[4,5,1-ij]quinolina2(1H)\text{-}ona\]

\[C_{17}H_{16}N_3O\]
**taplitumab paptuxum**
immunoglobulin G1, anti-(human antigen CD19) (mouse monoclonal B43 γ1-chain), disulfide with mouse monoclonal B43 κ-chain, dimer, disulfide with protein PAP (pokeweed antiviral)

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

**taplitumab paptuxum**
immunoglobulina G1, anti-(antígeno humano CD 19) (cadena γ1 del anticuerpo monoclonal de ratón B43), dimero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón B43, disulfuro con la proteína PAP (proteína antiviral de Phytolacca americana)

**tezacitabumin**
2'-deoxy-2'-(E)-fluoromethylene)cytidine

**tézacitabine**
4-amino-1-(2E)-2-(fluorométhylène)-2-désoxy-β-D-érythro-pentofuranosyl)pyrimidin-2(1H)-one

**tezacitabina**
2'-desoxi-2'-(E)-fluorometileno)citidina

\[
C_{10}H_{13}FN_2O_4
\]
tidembersatum

**tidembersat**

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

**tidembersat**

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

**tidembersat**

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

\[C_{20}H_{18}F_{2}NO_{4}\]

![Chemical structure of tidembersatum](image)

---

tilmacoxibum

**tilmacoxib**

\[4-(4\text{-cyclohexyl-2-methyl-5-oxazolyl})\text{-2-fluorobenzenesulfonamide}\]

**tilmacoxib**

\[4-(4\text{-cyclohexyl-2-méthyloxazol-5-yl})\text{-2-fluorobenzènesulfonamide}\]

**tilmacoxib**

\[4-(4\text{-ciclohexil-2-metil-5-oxazolil})\text{-2-fluorobencenosulfonamida}\]

\[C_{19}H_{18}FN_{2}O_{3}\]

![Chemical structure of tilmacoxib](image)
**tipifarnibum**

**tipifarnib**

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

**tipifarnib**

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

**tipifarnib**

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

\[\text{C}_{29}\text{H}_{22}\text{ClN}_{4}\text{O}\]

---

**tomeglovirum**

**tomeglovir**

\[N\text{-}[4-[[5-(dimethylamino)-1-naphthylsulfonyl]amino]phenyl]-3-hydroxy-2,2-dimethylpropionamide}\]

**toméglovir**

\[N\text{-}[4-[[5-(diméthylamino)naptalén-1-yl]sulfonyl]amino]phényl]-3-hydroxy-2,2-diméthylpropamidé\]

**tomeglovir**

\[N\text{-}[4-[[5-(dimetilamino)naftalen-1-il]sulfonil]amino]fenil]-3-hidroxi-2,2-dimetilpropanamida\]

\[\text{C}_{23}\text{H}_{22}\text{N}_{3}\text{O}_{4}\text{S}\]

---

---
traxoprodil

1-[(1S,2S)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]-4-phenylpiperidin-4-ol

traxoprodil

1-[(1S,2S)-2-hydroxy-2-(4-hydroxyphényl)-1-méthyléthyl]-4-phénylpipéridin-4-ol

traxoprodil

1-[(1S,2S)-2-hidroxi-2-(hidroxfenil)-1-metiletli]-4-fenilpiperidin-4-ol

\[\text{C}_{27}\text{H}_{36}\text{NO}_{3}\]

tridolgosirum

(1S,2R,8R,8aR)-octahydro-1,2,8-indolizinetriol

tridolgosir

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

tridolgosir

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

\[\text{C}_{17}\text{H}_{15}\text{NO}_{3}\]

valomaciclovirum

\(\text{L}\)-valine, 4-ester with 9-[(R)-4-hydroxy-2-(hydroxymethyl)butyl]guanine

valomaciclovir

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

valomaciclovir

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

\[\text{C}_{52}\text{H}_{59}\text{N}_{14}\text{O}_{4}\]
**vatalanibum**

vatalanib 1-(p-chloroanilino)-4-(4-pyridylmethyl)phthalazine

vatalanib N-(4-chlorophényl)-4-(pyridin-4-ylméthyl)phtalazin-1-amine

vatalanib 1-(p-cloroanilino)-4-(4-piridilimetil)ftalazina

\[ C_{26}H_{16}ClN_4 \]

**visilizumabum**


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

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

**ximelagatranum**


ximélagatran \( [(1R)-2-[(2S)-2-[4-\text{amino}(\text{hydroximino})\text{méthyl}][\text{benzyl}]\text{carbamoyl}]\text{azétidin-1-yl}]\)-1-cyclohexyl-2-oxoéthyl]amino)acétate \(\text{ d’éthyle}\)

ximelagatrán \( [(1R)-2-[(2S)-2-[4-\text{amino}(\text{hidroximino})\text{metil}][\text{benziloil}]\text{azetidin-1-il}]\)-1-ciclohexil-2-oxoetil]amino]acetato de etilo

\[ C_{36}H_{35}N_5O_5 \]
**zelandopamum**

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

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

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

\[C_{28}H_{28}NO_4\]

---

**ziralimumabum**

*ziralimumab*  
immunoglobulin M, anti-(human antigen CD147) (human monoclonal ABX-RB2 \(\mu\)-chain), disulfide with human monoclonal ABX-RB2 light chain, pentamer

*ziralimumab*  
immunoglobuline M, anti-(antigène CD147 humain) (chaîne \(\mu\) de l’anticorps monoclonal humain ABX-RB2), pentamère du disulfure avec la chaîne légère de l’anticorps monoclonal humain ABX-RB2

*ziralimumab*  
immunoglobulina M, anti-(antígeno CD147 humano) (cadena \(\mu\) del anticuerpo monoclonal humano ABX-RB2), pentámero del disulfuro con la cadena ligera del anticuerpo monoclonal humano ABX-RB2
AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 44

p. 184 adrogolidum
adrogolida
sustitúyase la descripción por la siguiente:
diacetato de (5aR,11bS)-4,5,5a,6,7,11b-hexahidro-2-propilbenzo[f]tieno[2,3-c]quinolina-9,10-diilo

p. 198 motexafinum
motexafina
sustitúyase la descripción por la siguiente:
9,10-dietil-20,21-bis[2-[2-(2-metoxietoxi)etoxi]etoxi]-4,15-dimetil-8,11-imino-3,6:16,13-dinitrilio-1,18-benzodiazacicloicosina-5,14-diildipropanol

p. 205 tanomastatum
tanomastat
sustitúyase la descripción por la siguiente:
ácido (2S)-4-(4'-clorobifenil-4-il)-4-oxo-2-[(fenilsulfanil)metil]butanoíco

p. 205 tebipenemum
tebipenem
sustitúyase la descripción por la siguiente:
2-pivalato y (4R,5S,6S)-6-[(1R)-1-hidroxietil]-4-metil-7-oxo-3-[(1-2-tiazolin-2-il)-3-azetidinil]sulfanil]-1-azabiciclo[3.2.0]hept-2-eno-2-carboxilato de metileno

Recommended International Nonproprietary Names (Rec. INN): List 45
Dénominations communes internationales recommendées (DCI Rec.): Liste 45
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 45
(WHO Drug Information, Vol. 15, No. 1, 2001)

p. 43 leredlimumabum
leredlimumab
replace the description by the following:
immunoglobulin G4, anti-(human transforming growth factor β2) (human monoclonal CAT-152 à 4-chain), disulfide with human monoclonal CAT-152 é-chain, dimer

leredlimumab
remplacer la description par la suivante:
immunoglobuline G4, anti-(facteur de croissance transformant humain β2) (chaîne à 4 de l’anticorps monoclonal humain CAT-152), dimère du disulfure avec la chaîne é de l’anticorps monoclonal humain CAT-152

leredlimumab
sustituyase la descripción por la siguiente:
immunoglobulina G4, anti-(factor β2 de crecimiento transformador humano) (cadena a 4 del anticuerpo monoclonal humano CAT-152), dímero del disulfuro con la cadena é del anticuerpo monoclonal humano CAT-152
Procedure and Guiding Principles / Procédure et Directives / Procedimientos y principios generales

The text of the Procedures for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances and General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances will be reproduced in uneven numbers of proposed INN lists only.

Les textes de la Procédure à suivre en vue du choix de dénominations communes internationales recommandées pour les substances pharmaceutiques et des Directives générales pour la formation de dénominations communes internationales applicables aux substances pharmaceutiques seront publiés seulement dans les numéros impairs des listes des DCIs proposées.

El texto de los Procedimientos de selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas y de los Principios generales de orientación para formar denominaciones comunes internacionales para sustancias farmacéuticas aparece solamente en los números impares de las listas de DCI propuestas.