RECOMMENDED INN LIST 40
INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES
WHO Drug Information

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Starting materials for pharmaceutical products: safety concerns

Many developing countries are wholly dependent on the importation of starting materials for use in the local production of essential and generic medicines. Starting materials are defined as those materials which are used in the manufacture of a pharmaceutical product or those which come into contact with the product during its manufacture. They may include raw materials, active and inactive ingredients, excipients, propellants, containers and packaging material.

Starting materials often change hands many times before reaching the manufacturer or assembler of the final marketed product and there are many opportunities for the material to undergo relabelling along the distribution and trade chain. As a result, chemicals and materials required for production of pharmaceutical products can become contaminated or undergo a change in identity, either accidentally or as a result of negligence, and sometimes fraud. For these reasons, it is important for the manufacturer to implement good manufacturing practices (GMP) and carry out analytical testing on all starting materials used in the production of pharmaceuticals.

The most documented incidents of contamination involve diethylene glycol, which is now held responsible for hundreds of unnecessary deaths throughout the world. Ingestion of diethylene glycol often leads to death through kidney failure. In Haiti in 1996, some 100 children died after taking paediatric syrup containing glycerol contaminated with diethylene glycol. International action is urgently needed to prevent similar incidents and tighten controls on the distribution, trade and manufacture of starting materials.

Perhaps the single, most important handicap to controlling starting materials stems from the practice of transshipment and multiple trading. Starting materials invariably pass through the hands of agents or traders, and can be repackaged and relabelled at any stage of the distribution chain. By the time a container has reached its destination, it may no longer have an accurate description of its contents either on the labelling or the certificate of analysis which accompanies it. Substitution of a cheaper, substandard, more easily available product is, of course, of financial benefit to the supplier — but it can have a tragic effect on the health of the consumer.

Given the need for immediate action, a meeting was recently convened by the Division of Drug Management and Policies of the World Health Organization on the control and safe trade in starting materials for pharmaceuticals. Participants from regulatory authorities, nongovernmental organizations, consumer organizations and representatives of the major pharmacopoeias as well as inspectors, pharmacists, traders, customs officials and chemical and pharmaceutical manufacturers, were invited. The meeting formulated several recommendations which are set out on page 134.

Glycerol contaminated with diethylene glycol

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In Haiti, between November 1995 and June 1996, 88 children died of acute renal failure after taking locally manufactured paracetamol (acetaminophen) elixir, an anti-fever syrup. A major component of the syrup is glycerol (USAN: glycerin), which was later found to have been contaminated with approximately 20% diethylene glycol (DEG). DEG is an industrial chemical not intended for pharmaceutical or food use which can cause severe kidney damage when ingested.

In June 1996, the US Food and Drug Administration (FDA) and the US Centers for Disease Control and Prevention (CDC) in collaboration with the Pan American Health Organization (PAHO) and the Haitian Ministry of Health, identified DEG in two brands of paracetamol syrup available in Haiti. The FDA was requested to assist in the investigation of this product and its manufacture.
The two brands of paracetamol syrup in question were available in either 4-ounce bottles or as oral drops for neonates in 2-ounce bottles; both had identical formulations. The syrup was found to contain 12–17% DEG and the oral drops contained 3–5% DEG. One shipment of glycerol was used in five lots of the paracetamol. Later FDA analysis of residue left in two drums suspected to originate from the glycerol shipment showed 16–24% DEG, 32% water, 23% sugar and 1–4% of the labelled glycerol in one drum and 26% DEG in the second drum.

Further investigation revealed that the manufacturer of the finished dosage form did not test the raw materials upon delivery, had no in-process quality control, and no finished product testing other than pH. Because of inadequate recording and lack of manufacturing controls, it was impossible to establish which lots of the finished product were manufactured from the contaminated glycerol shipment. The company recalled all products which contained glycerol.

The FDA investigators traced the glycerol by visiting the shipper in the Netherlands. This disclosed that the glycerol was shipped from the Netherlands, but the shipping record showed that the product was billed through a company in Germany. Records of the German company disclosed that the glycerol originated in China. A sample of the glycerol held by the company in the Netherlands was collected by FDA officials and analysed. The analysis disclosed 11% glycerol and 21% DEG.

Previous analysis of the shipment of glycerol to Haiti showed a purity of 53% rather than 95%, as reflected on the invoice. This information was communicated to the distributor in China who handled the sale of glycerol, with information that a second sample would be taken for further analysis. The distributor in China did not receive the results of the second analysis: by then, the shipment was already on its way to Haiti.

With assistance from the US Embassy in Beijing, FDA officials visited the distributor and manufacturer in China. Between 1993 and 1995, the glycerol was manufactured by a fermentation process and glycerol was the company’s only product. At the time of the investigation in November 1997, the company had moved to a new plant and the records, which are normally kept for one year, had been destroyed.

The carbon source of the fermentation media was cane sugar and DEG was not used for the production of glycerol. Purification would bring the concentration to 95, 96 or 98% depending on the grade of glycerol being made. The glycerol was tested to meet USP 21 by both the company and the distributor, but the original certificate of analysis of these tests was not available.

It is hoped that the informal consultation recently held by WHO on the control and safe trade in starting materials will emphasize the importance of the safety and quality of pharmaceutical starting materials such as glycerol and will provide the approach and exposure necessary to prevent future incidents such as the Haiti tragedy.

Pharmaceutical excipients: certificates of analysis and vendor qualification

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Before purchasing or trading in excipients or other starting materials takes place, it is common practice within the pharmaceutical industry to request a certificate of analysis (COA). A COA relates specifically to the results of tests carried out on a representative sample drawn from the material to be delivered and will contain information on the results of analytic and performance tests, thereby providing a trustworthy indication of the quality of the material to be supplied. COAs are of significant value when properly used.

Experience shows, however, that these certificates are not always accurate or reflective of the material they describe, and when this occurs the situation can become dangerous. Because COAs appear to be official, the information they contain is accepted as valid and decisions are made based on the data they contain. However, when false information is provided on the quality of the material, it can lead to serious complications. From the public health perspective, a product that has a severely reduced or no therapeutic value can have negative consequences for the consumer and, if the product fails, can represent a significant loss in investments and reputation.

The company in Haiti described in the previous report, accepted a shipment of glycerol and used it
to manufacture their product on the basis of information provided in a COA, only to discover that it was heavily contaminated with diethylene glycol. Subsequent investigation showed that the data contained in the COA did not correspond to results of analysis of the material in question.

As a result of this and similar incidents, the International Pharmaceutical Excipients Council (IPEC) has developed the *Good manufacturing guide for bulk pharmaceutical excipients* (1) to qualify vendors and set out basic requirements for the manufacture, packaging, storage, and testing of material. The Guide was compiled in collaboration with WHO and closely follows the *WHO good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients* (3). Application of the advice contained in this simple guide would have prevented the tragic incident in Haiti.

Two basic principles are set out in the guide. Firstly, the manufacturer of the final pharmaceutical product is ultimately responsible for the safety and quality of that product. Secondly, a certificate of analysis must reflect the actual results obtained or observed for both qualitative and quantitative data. The COA should additionally include the name of the company, where the material was manufactured, and the signature of a person within the company having authority to attest to the results. The guideline clearly states that compliance with standards and specifications established for excipients, either through the national or regional pharmacopoeia or by a user or manufacturer of an excipient, are insufficient to assure the safety, purity, and key characteristics of the material. In order to supply this information, performance tests are also needed.

Chemical analyses have now attained new levels of precision and sensitivity, advances in chromatography have permitted new and more rigorous definitions of purity, while dissolution tests and bioavailability-bioequivalence studies of drug products have raised questions concerning the potential impact that excipients may have on the product and the importance of the consistency of their characteristics. The SUPAC Guidelines established within the United States by the Food and Drug Administration (2) contain minimum requirements to ensure that any potential changes during manufacture of the final drug product are appropriately transparent and adequately controlled.

Despite advances in technology, one principle remains uncontested. Quality can only be "built in": it is only through consistent adherence to good manufacturing practices (GMP) that the safety, purity and consistency of the excipient can be assured. The guideline recommends that once a supplier is identified as a source or potential source of material to be used as an excipient, the manufacturer should confirm the supplier’s ability to adhere to GMP. Should the supplier turn out to be a distributor, adherence to GMP by the manufacturer will need to be confirmed. It is important to know if all operations are performed by the manufacturer, if subcontractors, such as contract packagers, are used, or if the material is sold to repackagers prior to acquisition by the company responsible for the final product. In the event that contractors or repackagers are used, their adherence to GMP should be confirmed. If the excipient distributor or manufacturer is found to have an adequate GMP programme this may be used to confirm adherence to GMP, which should then be periodically reconfirmed.

If the material is set out in the relevant pharmacopoeia, the manufacturer’s tests and specifications must conform to pharmacopoeial or other national requirements. If a modified or non-pharmacopoeial method is used, the method must be validated to ensure that results are reliable and equivalent to requirements. In accepting a COA the following criteria must be met:

1. The supplier’s ability to adhere to GMP should be confirmed.
2. Analytical methods should be identical or validated as equivalent throughout all testing.
3. An adequate number of batch samples should be evaluated to compare results with those contained in the COA. Results for quantitative assays must be comparable and within specifications. For tests other than quantitative assays, all results must be within specifications.
4. Any material qualified by the above procedure should be periodically subjected to complete testing to reconfirm the reliability of the supplier’s COA results.

Finally, an agreement should be formalized as part of the procurement procedure stipulating that all material must be traceable during its life cycle, and
that the user will be notified in the event of any significant changes in procedures and quality of the material.

As can be seen, the information contained in the COA needs to be confirmed by a testing laboratory. However, some pharmaceutical companies may not have laboratories equipped to perform these tests. In such circumstances, it is recommended that an independent central laboratory be utilized for this purpose. It is only through correct analysis that the suitability of the material can be confirmed.

As a continuation of the guidance document procedures, IPEC is currently working on more detailed guidelines covering some of the key steps for qualifying vendors. It is anticipated that the majority of these projects will be completed during 1999. In the meantime, the Guide establishes a basic framework for determining the suitability of starting materials.

References
1. Good manufacturing practices guide for bulk excipients published by The International Pharmaceutical Excipients Council and available from: Dr E. Izeboud, IPEC Europe, Kerkweide 27, 2265 DM Leidschendam, Netherlands. email: eizeboud@worldonline.nl or Mr L. Blecher, IPEC Americas, ISP, 1361 Alps Road, Bldg 3, Wayne, NJ 07470, USA.
2. Guidance for industry: Scale-Up and Post Approval Change (SUPAC) Expert Working Group, Chemistry Manufacturing Controls Coordinating Committee, Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, USA.

Quality assurance and supply of starting materials
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Given today’s level of sophistication in analytical methodology, fatal events resulting from contamination of starting materials used in pharmaceutical products are unacceptable. Concepts such as good manufacturing practices (GMP) and Total Quality make incidents involving contamination of glycerol with diethylene glycol difficult to comprehend.

Good manufacturing practices lay out the ground rules for the pharmaceutical industry, and tools are available for application throughout every component of the supply chain. The decision not to use the tools, or the casual and careless use of them, is inexcusable. The following practices reflect efforts undertaken by the pharmaceutical industry to avoid situations such as that which has occurred in Haiti.

Sampling procedures
The classical approach to quality assurance of starting materials is based on a sampling procedure in preparation for testing and release. Starting materials should meet predetermined compliance specifications using prescribed methods. The process involves a carefully designed sampling method to assess the level of purity and check for the absence of foreign matter. A company will typically create standard operating procedures based on this method and an overall sampling plan will also be drawn up to permit the statistical interpretation of data. These two elements combined will ensure with confidence that the material present in an array of containers is of uniform quality and free from unwanted contamination.

No matter how well designed the sampling process and interpretation of guidelines, a guarantee can never be obtained that the material to be used is totally free of foreign matter. However, for a material to be as clean as possible, the sampling performance skills of trained personnel are important. The ability to remain focused and observant during the task will provide an increased level of confidence. Anything that appears different or unusual, such as a broken or missing seal, different outer packaging, material clumping, strange appearance, or odour not observed on previous occasions — can provide important indicators of the need for specific additional analysis and, perhaps, an increased sampling regimen.

In addition to the importance of ensuring that the sample or series of samples statistically represent the delivery as a whole, the environment in which the sampling takes place should be considered. Facilities must be arranged in such a way as to eliminate the possibility of incorporation of unwanted contaminants into the material being sampled. Isolation compartments and the use of filtered air provide such an environment and should be considered as mandatory for certain materials.

Upon completion of sampling, adequate records are made of the sampling process, and the appropriate
records and labels are filled out and affixed to containers to provide ease of traceability at a later date. The samples are then taken to the quality control laboratory for testing.

**Quality control testing**

During quality control testing, only standard analytical equipment and validated methods should be used. In order to remain within budget limits, cost and time of testing require strict rationalization. This must be based on scientific appropriateness and sound judgement and must not compromise the appropriate interpretation of quality. In order to successfully apply this rationalization process, the industry has devised a tracking system to plot the analytical results of successive batches of material purchased from the same vendor or manufacturer over time. This tracking allows the individual quality control unit to evaluate whether reduced testing programmes can be applied in light of the quality of the material being provided.

When used in collaboration with a supplier certification programme, reduced testing will cut costs without compromising quality. This is of value in the effective and efficient use of resources. Whether the samples brought to the laboratory for quality testing are subjected to full testing or to reduced testing, strict adherence to instructions must be observed. In Haiti, if the sample of glycerol contaminated with diethylene glycol had been subjected to the USP titration method, it would have failed the assay and would have been rejected as not reaching acceptable standards for use in the manufacture of a pharmaceutical product.

**The need for built-in quality**

The most important objective of GMP is to ensure that quality is built into a product. This cannot happen after end-user quality control testing has identified the sample as unacceptable. Thus, attention should be paid to product quality throughout the manufacturing process, with particular attention to purification methods or controls designed to eliminate introduction of impurities. Specific efforts should be made to avoid contamination during sampling and any opening of containers or handling of material should be undertaken with caution. It is also important that packaging and repackaging should be considered as part of the manufacturing process as well as a pharmaceutical operation.

Supplier qualification is an important and logical system and auditing a supplier provides evidence of the vendor’s capability to consistently produce and assure the intended and specified quality of the respective product or starting material. Confidence in reliable customer service, including quality of products and conditions of delivery can only be built up over time.

A supplier certification programme provides an innovative opportunity to formalize collaborative relationships between vendor and purchaser. This is not a new concept, and such programmes make good sense. They are readily applicable to finished products and active ingredients which have a clearly defined use. However, it becomes more complex when starting materials are at issue which are not particularly destined for pharmaceutical use. Vendors cannot be expected to alter their operating mechanisms when the pharmaceutical industry represents a small percentage of the total customer portfolio. In such cases, where GMP is not applied throughout the manufacturing process, other quality management systems — such as ISO 9000 series — may be useful, although not equivalent to analysis and GMP, in providing a basis for customer-supplier information.

In many cases, international pharmaceutical companies are associated with a parent chemical company or are themselves manufacturers of several chemicals, whether as active or inactive ingredients. In this situation, supplier certification programmes and production and control to the same level of quality is not only possible but is a logical operating requirement.

Manufacture, quality assurance and documentation in accordance with GMP are key factors in the successful operation of pharmaceutical production. An efficient response to quality failure reports is possible only if the contents of all batches are traceable and identifiable. It must be remembered that the responsibility for the quality, safety and efficacy of a marketed product will ultimately fall on the marketing authorization holder.

As we move into the next millennium and witness the emergence of even larger industrial conglomerates, we must be vigilant and foster effective communication with supply partners. Through careful definition of requirements, suppliers can better serve the needs of the pharmaceutical industry and help provide better and safer medicines.
Implementation of vendor certification

Within the pharmaceutical industry, there has been considerable interest in establishing and implementing vendor certification, and a number of companies have grouped together to explore the potential. As a result, guidelines for vendor certification were established in 1989 by the Pharmaceutical Manufacturers Association (PMA)* with the intention of assisting member firms and their suppliers in setting up a certification programme. The guidelines also define terminology and describe the concepts to be considered.

The guidelines apply to bulk pharmaceutical chemicals and raw materials, drug product components, containers, closures and other packaging materials, currently referred to as starting materials. They list the critical elements which make up a successful vendor certification programme. However, becoming certified requires many kinds and different levels of effort from the many parties involved. Furthermore, circumstances may vary depending on the type of operation, the nature of the process involved, or product standard requirements — so that a certain amount of latitude and judgement is an essential component in implementing the guidelines.

Vendor certification constitutes an important component of a total quality management system to ensure that a product is manufactured, assembled, packaged and shipped under a controlled process that results in consistent conformity with customer requirements. It is based on the principle of defect prevention as opposed to defect detection and selection. It supports the concept of quality at the source by correct application of procedures and elimination or reduction of the need for final quality inspections by the customer. If successfully implemented, vendor certification should improve quality and delivery performance, increase productivity, and reduce costs.

Control and safe trade in starting materials for pharmaceuticals: recommendations

As a result of the tragic incident in Haiti and similar situations which have occurred previously throughout the world, a meeting on the control and safe trade in starting materials for pharmaceuticals was organized by the Division of Drug Management and Policies, at WHO Headquarters, Geneva, from 25 to 27 May 1998. The purpose of the meeting was to evaluate the international public health impact of these events and to forge ways in which to prevent similar incidents from occurring in the future.

As an intergovernmental organization, WHO is in a unique position to provide a global forum for discussion of the problem of contaminated and substandard pharmaceuticals. The meeting, which was made up of the major interested parties, proposed the following recommendations.

All parties should:

• Ensure that starting materials meet quality control requirements.
• Ensure that starting materials meet the labelled pharmacopoeial requirements.
• Ensure that starting materials are manufactured, handled and distributed in accordance with good manufacturing practices.
• Collaborate in the free and unbiased exchange of information.

National authorities should:

• Extend legislation to include all starting materials.
• Ensure that all parties manufacturing or handling starting materials or pharmaceutical products are legally authorized to carry out such an activity. Appropriate sanctions should be established in the event of failure to comply with national regulations.
• Monitor GMP compliance through regular inspection, and extend inspection to free ports.

*PMA Guidelines for vendor certification. Available from Pharmaceutical Research and Manufacturers of America (PhRMA), 110 15th Street, NW, Washington DC 20005, USA. Fax: 001-202-835-3597 e-mail: twhite@phrma.org
• Ensure that a fully equipped and accredited national quality control laboratory is available.

• Only allow use of starting materials where facilities for analysis and performance testing are available.

• Extend regulatory approval procedures to cover excipients, and include excipients in drug master files.

**Manufacturers should:**

• Ensure that production plants contain or have access to an analytical testing laboratory to control the quality of starting materials and related products.

• Ensure access to a fully equipped and accredited quality control laboratory before producing or handling sophisticated materials.

**Traders should:**

• Establish a national trade association.

• Only accept materials which are manufactured in accordance with GMP.

• Ensure that starting materials are traceable at all points in the distribution chain and keep records, in particular of any relabelling.

**WHO should:**

• Issue guidelines on the correct use and application of certificates of analysis (COA).

• Only support local manufacture which is carried out according to GMP.

• Develop an international nomenclature system for excipients.

• Develop a model for risk assessment of starting materials and identify high risk starting materials.

• Encourage development of skills for personnel handling or dealing with starting materials.

• Extend the WHO Certification Scheme to cover all starting materials.

• Continue to develop simple alternative test methods for inclusion in the *International Pharmacopeia*.

• Develop guidelines on requirements for the purchase of starting materials.

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*A report of the meeting on the control and safe trade in starting materials for pharmaceuticals is available from the Division of Drug Management & Policies, World Health Organization, 1211 Geneva 27, Switzerland.*
Reports on Individual Drugs

Tamoxifen in the prevention and treatment of breast cancer

When diagnosed in time, breast cancer and all detectable cancer tissue can be removed surgically. However, because micrometastatic deposits of the disease can remain, adjuvant tamoxifen is routinely administered immediately following surgery. Although this practice has been shown to improve the 10-year survival rate of patients (1), uncertainty remains concerning which patients should receive treatment, and for how long.

In order to clarify this issue, the Early Breast Cancer Trialists Collaborative Group (EBCTCG) has carried out a meta analysis of 55 clinical trials conducted in 15 countries and involving 37 000 women diagnosed with early breast cancer (2). Results of the study showed that, when tamoxifen is started immediately following surgery and irrespective of age, relapse is prevented in 1 in 6 women and mortality in 1 in 12.

Furthermore, 5 years of tamoxifen therapy significantly reduced breast cancer recurrence by 42% and mortality by 22%. These results were similar for women under 50 years of age and older women. Among women who had received both chemotherapy and adjuvant tamoxifen for five years, 61% had no recurrence of disease after ten years, compared with 40% who were receiving chemotherapy alone. The results also showed an almost 50% reduction in new cancers in the contralateral breast during five year tamoxifen therapy.

However, for the 8000 women who had low or zero level estrogen-receptor protein in the primary tumour, the overall effects of tamoxifen appeared to be small. In the light of these results, the authors conclude that for women with estrogen receptor protein negative tumours, the benefit of adjuvant tamoxifen is not yet proved.

A recent clinical trial on the prophylactic use of tamoxifen in healthy women with a family history of breast cancer was terminated 14 months early when it was shown that tamoxifen reduced breast cancer incidence by 45% across all age groups compared with placebo. The trial, run by the National Cancer Institute and the National Surgical Adjuvant Breast and Bowel Project in the United States of America, was scheduled to last six years, and involved over 13 000 women (3).

It remains to be seen from the results of these latest trials, whether genetic screening for women at high risk for breast cancer might be beneficial in identifying those in need of prophylactic therapy (4).

References


Selective serotonin re-uptake inhibitors and withdrawal reactions

Selective serotonin re-uptake inhibitors (SSRIs) are a relatively new class of antidepressants. Although the first product in this family of drugs was introduced as early as 1982, a significant increase in the use of SSRIs was observed only when fluoxetine, the third drug of this family, was launched in 1988 under the brand name, Prozac®. The success of fluoxetine resulted in a rapid expansion of the antidepressant market and, during the 1990s, additional SSRIs such as sertraline, paroxetine, venlafaxine, citalopram and nefazodone were also marketed.

However, despite a general belief that SSRIs did not create dependence or lead to symptoms of withdrawal when discontinued after long-term use, it was not long before case reports of withdrawal symptoms were received. The first reported case
involved a 32-year-old man who had experienced agitation, inability to concentrate and insomnia within 48 hours of discontinuation of fluoxetine (1). In the following year, a case was reported of a 30-year-old woman, treated with fluvoxamine 100 mg/day, who was overwhelmed by strong feelings of aggression when she tried to stop taking the medication (2). Similar isolated case reports continued to be received.

In an open study, when 14 patients were withdrawn from fluvoxamine after 7–8 months of treatment, new symptoms developed in 12 of the patients. These included dizziness, incoordination, headaches, nausea and irritability, and were distinguishable from the panic disorder for which the drug was prescribed. Symptoms usually peaked on day 5 after withdrawal (3).

Reports of withdrawal symptoms did not exclude the newer SSRIs. In 1993, the British Committee on Safety of Medicines cited 78 reports of symptoms occurring upon withdrawal of paroxetine, including dizziness, sweating, nausea, insomnia, tremor and confusion (4). A case of sertraline withdrawal was reported in 1994 (6) and the first reports on venlafaxine withdrawal were published two years later, citing such symptoms as muscle aches, fatigue, headache, nausea and dizziness (6). A substitution study suggested that nefazodone would not be an exception (7).

Isolated case reports of withdrawal symptoms associated with individual SSRIs have been supported by a number of observations. Several recent studies compare spontaneous reports of withdrawal symptoms from different SSRIs collected by adverse drug reaction monitoring programmes. According to data on adverse drug reactions from the United Kingdom, the rates of withdrawal reaction reports were different for different SSRIs: 0.3 per 1000 prescriptions for paroxetine, 0.03 per 1000 for sertraline and fluvoxamine, and 0.002 per 1000 for fluoxetine (8).

Drug surveillance data from France indicate that withdrawal reactions with fluvoxamine and paroxetine occur in a greater proportion of reports than with fluoxetine (9). A careful review of the WHO adverse drug reaction data base in relation to drug sales statistics converted into DDDs (defined daily doses) reveals that the reporting rate of withdrawal reactions for paroxetine was higher than that for sertraline and fluoxetine in Australia, the United Kingdom and the USA, which were selected for detailed analyses, as well as for all 16 reporting countries combined (10). With an increasing number of reports of this kind, SSRI withdrawal has become the topic of several review papers. Although an early review concluded that withdrawal symptoms associated with the discontinuation of fluoxetine had not been established (11), more recent reviews explain the lower incidence of fluoxetine withdrawal symptoms in relation to its long half-life, the incidence appearing higher with shorter half-life agents (12). Common physical withdrawal symptoms appear as problems of balance, gastrointestinal and flu-like symptoms, and sensory and sleep disturbances. Psychological symptoms include anxiety, agitation, crying spells, and irritability. Some symptoms are similar to those reported with discontinuation of tricyclic antidepressants. However, SSRI discontinuation is also associated with novel symptom clusters, including sensory abnormalities and possibly aggressive and impulsive behaviour (13).

The clinical implications of SSRI withdrawal should be considered in the context of duration of treatment, clinical management of withdrawal, and risk of dependence and abuse. Because the symptoms of SSRI discontinuation include changes in mood, appetite and sleep, they are sometimes mistaken for signs of a relapse into depression (14). This can lead to continued prescribing even after depression has been treated. With regard to clinical management of withdrawal, gradual tapering is recommended, particularly for short half-life SSRIs (15). Concerning the risk of dependence and abuse, opinions are mixed. Some reviewers consider that SSRIs are not associated with dependence or drug-seeking behaviour. However, the same authors noted that SSRI discontinuation symptoms could be troublesome and there were several case reports where symptoms occurred consistently despite repeated attempts to taper therapy (12).

There is obviously some confusion about the concept of dependence in such discussions. The simplest definition of drug dependence given by WHO is "a need for repeated doses of the drug to feel good or to avoid feeling bad" (16). When the patient needs to take repeated doses of the drug to avoid the bad feelings caused by withdrawal reactions, the person is dependent on the drug. Those who have difficulty coming off the drug even with the help of tapered discontinuation should be regarded as dependent, unless a relapse into depression is the reason for their inability to stop the antidepressant medication.
In general, all unpleasant withdrawal reactions have a certain potential to induce dependence and this risk may vary from person to person. Dependence will not occur if the withdrawal reactions are so mild that all patients can easily tolerate them. With increasing severity, the likelihood of withdrawal reactions leading to dependence also increases. Although reporting rates of SSRI withdrawal are low in comparison with prescribed doses, it is prudent to recommend the monitoring of patient withdrawal symptoms even when SSRIs are prescribed at modest doses (17).

References


Triclabendazole and fascioliasis

It is estimated that 2.4 million people suffer from fascioliasis infections worldwide, and a further 180 million are at risk of infection. Outbreaks can cause severe illness, and in some areas over 60% of the population can be infected. Typical symptoms include fever, abdominal pain, gastrointestinal disturbances, urticaria, hepatomegaly, anaemia and jaundice caused by the inflammatory response and lesions in the abdominal cavity and liver.

The liver flukes Fasciola hepatica and F. gigantica are flat worms which live in the bile ducts of their definitive hosts: either ruminants or man. Infection occurs through consumption of uncooked aquatic vegetables which have been contaminated with encysted parasitic larvae. Larvae migrate from the small intestine, across the intestinal wall, into the abdominal cavity. Within 24 hours of ingestion, the larvae have become immature worms and move to the liver to feed on liver tissue. While in the bile ducts, the worms mature into adult form. Each produces eggs which are then released into the biliary passages and are shed in the faeces.

Until recently, treatment of fascioliasis has been difficult because praziquantel — effective against most trematode infections — is inactive against...
Fasciola species. Triclabendazole has been used effectively in veterinary practice for fascioliasis since 1983 and, following its successful use in humans during an outbreak in 1989 in the Islamic Republic of Iran, WHO concluded an agreement with the company Ciba-Geigy (now Novartis) to undertake human clinical studies to evaluate its effect. As a result of this agreement, a development programme of clinical trials in Bolivia, Chile, Cuba, the Islamic Republic of Iran and Peru has now been successfully concluded.

The most efficient dosage of triclabendazole for this indication was demonstrated to be 10 mg/kg given in two equal doses. During all trials, the drug was well tolerated and cases of transient biliary obstruction were attributed to the accumulation of dead worms during treatment. Triclabendazole was demonstrated to be highly efficacious and was not associated with serious adverse effects. As a result, the drug has been included in the WHO model list of essential drugs. On a population basis, treatment provides immediate relief to infected individuals and reduces the prevalence and intensity of the disease burden.
Current Topics

Reverse transcriptase activity in vaccines

Reverse transcriptase is an RNA-dependent DNA polymerase enzyme. Although such enzyme activity is also known to derive from other sources, it is generally related to the group of viruses known as retroviruses. Because the replication cycle of retroviruses involves a double-stranded DNA copy of the viral genome which integrates into the chromosome of the host, most animal and avian species contain evolutionary remnants of ancient infections as part of their genetic make-up. These remnants are known as endogenous proviral genomes or retroviral-like elements and generally they no longer encode a functional viral genome. Thus, the presence of genes for reverse transcriptase in the absence of infectious virus has been identified in a variety of mammalian and avian cells.

Many vaccines are produced using chicken embryo cells, and these should be derived from closely monitored specific pathogen free (SPF) flocks which are free of infectious avian retroviruses, in compliance with WHO requirements (1). The tests for retroviruses include assays for reverse transcriptase (RTase) and, based on the newer nucleic acid amplification techniques, several laboratories have developed assays with improved sensitivity. Application of these more sensitive assays (2) has detected low levels of RTase in vaccines produced using chicken embryo cells, including live attenuated vaccines for measles, mumps and yellow fever which have been manufactured in compliance with WHO requirements. No such activity has been reported in vaccines produced using human diploid cells (2, 3).

The detection of low levels of RTase in vaccines derived from chicken cells has given rise to concern that a previously unidentified avian retrovirus could be present in vaccines prepared using chicken cells. The results of laboratory and other investigations were first reviewed by a group of experts at a WHO Consultation in 1995 and by the WHO Expert Committee on Biological Standardization (ECBS) in 1996 which concluded that WHO requirements (1) continue to be appropriate and that there was no evidence to suggest that the presence of RTase has any medical significance for humans (5). Much work has been undertaken since and, in April 1998, WHO convened a follow-up meeting of experts in virology, vaccine production and epidemiology to review the latest scientific data (5).

Most recent studies indicate that the RTase activity found in chicken cells and in derived vaccines is associated with particles. This particle-associated RTase activity is common to all chicken cells and is not related specifically to vaccines. Notwithstanding, it was recommended that further studies should be undertaken to clarify the reason for the presence of low levels of RTase activity in cell substrates which are used in the manufacture of vaccines and other biological products. WHO will set up a task force of scientists, regulatory authorities and specialists from industry to conduct collaborative research on the characterization, quality control and safety assessment of all cell substrates intended for vaccine production.

The meeting concluded that the risk of vaccine-preventable disease is real and quantifiable, and should supervene the theoretical and remote risk posed by RTase activity in chicken cell derived particles. Vaccines, such as those against measles, have a long and safe record of extensive international use and their beneficial effects in preventing mortality and morbidity are well established. It was therefore recommended that chicken cell derived vaccines, which have a major role in international immunization programmes, should continue to be used.

Moreover, it was considered that the cell substrate used in the production of a live vaccine is a critical parameter in the level of attenuation or virulence of live vaccine viruses. If the cells used for production are changed, there could be unknown effects on the safety and efficacy of these vaccines. Thus, any alternative cell substrate developed for the production of a live viral vaccine would be considered as novel development. In this case, the vaccine would need to be resubmitted for regulatory approval, thereby halting the continued production of vaccines which are urgently needed for public health programmes.
References

1. WHO Expert Committee on Biological Standardization. 

2. World Health Organization. Requirements for measles, 
mumps and rubella vaccines and combined vaccine (live). 
In: WHO Expert Committee on Biological Standardization: 
fourty-third report. WHO Technical Report Series, No. 840, 
1994.

transcriptase activity in live attenuated virus vaccines. 

4. Bauer, G., Hofschneider, P.H. An RNA-dependent DNA 
polymerase, different from the known viral reverse 
transcriptases, in the chicken system. Proceedings of the 

5. World Health Organization. Consultation on issues 
related to the presence of reverse transcriptase activity 
and chicken-cell derived vaccines. Unpublished document 
WHO/BLG/RTASE 98.1.

Consumer protection and 
herbal remedies

Mohamed H. Farah
Uppsala Monitoring Centre
Sweden

The use of herbal remedies has increased signifi-
cantly in developed countries in the last decade, 
and this trend shows every sign of continuing. 
Herbal preparations have recognized medicinal 
value, and many are free of the problems associ-
ated with some synthetic pharmaceuticals. Because 
they have been used to treat illness for hundreds of 
years, it is assumed that they must be safe. How-
ever, with the rise in popularity and increased use it 
is necessary to assure product quality and safety 
and implement regulatory control of the manufactur-
ing process and licensing of traders.

An essential element in the quality assurance of 
herbals is the correct identification of a product. 
This may be difficult to achieve since, in many 
cases, a common, local name is used. Alternatively, 
the product may have been adulterated or substi-
tuted by other mixtures. There may be no routine 
tests to monitor the intended amounts of active 
ingredient before and after processing. A single 
species may be known by different Latin names 
and also by many common names which can vary 
from country to country.

Moreover, it is not unusual for a common name to 
be used for two or more different species. Unless 
the names of herbal plants follow an international 
system of plant nomenclature, the potential for 
collision when exchanging information is enor-
mous. The information attached to a name is thus 
Crucial. As an example, because common names 
are often used, heliotrope (Heliotropium 
europeum) — containing potent hepatotoxins — is 
often confused with garden heliotrope (Valeriana 
officinalis), which is used as a sedative and muscle 
relaxant. Identification of the herbal preparation by 
the Latin binomial system, in addition to the com-
mon name, is therefore essential.

When administering herbals, the dose of an active 
substance determines its usefulness and safety. 
Manufacturing controls are therefore important to 
determine potency and manufacturers of herbal 
remedies should develop international standards of 
identity and quality control. In order to regulate 
unrealistic claims on retail products, labelling and 
advertising should comply with accepted criteria for 
promotional practice.

A review of medical literature will often fail to pro-
vide full information on the safety and efficacy of 
the overwhelming majority of herbal remedies. 
Adverse effects vary greatly, and will depend on the 
particular species of plant, when and how it is 
harvested, the part of the plant being used and how 
the plant material is processed. The Uppsala Moni-
toring Centre in Sweden has recently begun collect-
ing data on the safety and toxicity of herbal medi-
cines from all over the world. These data are of 
immediate relevance to health professionals and 
producers of herbal medicines.

The Centre represents a component of the WHO 
International Drug Monitoring Programme which is 
made up of over 50 national monitoring centres. 
Reports of suspected adverse reactions to pharma-
ceuticals, vaccines and, now, herbal remedies are 
sent by health professionals to national monitoring 
centres and from there forwarded to the data base 
located at the Centre. With more and more coun-
tries joining the programme, the number of reports 
of adverse reactions to herbal preparations is 
increasing. However, to be able to effectively 
monitor the safety of all herbal medicines, the 
reporting system has to be developed further and 
reporting should be promoted among health profes-
sionals.
Any physician who has a patient taking a particular herbal medicine should document and report any clinical events which may result. If the patient is also taking a prescription medicine, interactions must be noted. If any of the active ingredients is expected to act in an antagonistic or synergistic manner, an alternative medication should be sought or the herbal remedy changed.

In order to enter information into the data base, an ATC (anatomical, therapeutic, chemical) classification is being developed. Several international experts and centres, including the Royal Garden at Kew in the United Kingdom, are involved in setting up the data base. It is hoped that in the future a monograph will be available for each plant species or active part of a plant.

It is very important that regulations on herbal medicines should clearly distinguish between plants which can safely be used under most circumstances and at reasonable quantities, and specific herbs with potent, addictive, or otherwise dangerous properties.

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Information on the data base can be obtained from: Uppsala Monitoring Centre, S75320 Uppsala, Sweden. e-mail: who.drug@who.pharmasoft.se; internet: http://www.who.pharmasoft.se

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**Indiscriminate antibiotic use in animals — public health implications**

The frequency of resistant bacteria and the number of drugs to which they are resistant is increasing at an unprecedented rate and has begun to compromise the efficient treatment of patients. Although the gravity of the problem has been brought to the attention of governments, industry and the general public, action is urgently needed if the problem is not to escalate into a full-scale public health disaster.

Reports of importation into the United Kingdom of *Escherichia coli* resistant to all beta-lactam antibiotics (1) further demonstrate that antibiotic resistance knows no boundaries. A recent study has shown that the prevalence of multidrug-resistant salmonella infections in the United States of America has increased from 0.6% in 1980 to 34% in 1996 (2). The trend is the same for other countries, as confirmed by a recent report from the Select Committee on Science and Technology commissioned by the House of Lords in the United Kingdom (3). Isolates that were already resistant to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracycline were found to be 14% resistant to ciprofloxacin and 24% resistant to trimethoprim in 1996. This finding was even more striking because there was no resistance five years previously in 1991 (4). An analysis of approximately 25 000 pathogens by the SENTRY antimicrobial surveillance programme indicated a 46% rate of penicillin-resistant *Streptococcus pneumoniae* in the USA and a rate ranging between 0.1 and 30% in European countries.

Two major factors contribute to antibiotic resistance, namely, the antibiotic itself and the type of resistance traits under selection (5). As a further complication, these traits can be spread among different bacteria. Resistance displayed by bacteria reflects the environment in which the organism thrives and genes that have been prevalent in pathogenic bacteria for many years develop point mutations conferring resistance to broad-spectrum antibiotics.

Certain antimicrobials used for treatment or growth promotion in agriculture are also used for disease control in humans and it has been estimated that more than 50% of antimicrobials are produced for purposes other than human medical use. In the United States, of the 23 million kilograms of antibiotics produced annually, over 40% are for animal use. Of this amount, 80% is used subtherapeutically as a growth promoter. The use of antibiotics at subtherapeutic concentrations to enhance growth in animals and for farming purposes has increased resistance (5). Animal use of avoparcin, a glycopeptide growth promoter is, at least in part, responsible for the emergence of vancomycin-resistant enterococci in animals and the same vancomycin-resistant clone of enterococci has been found in animals and humans (6). These findings have led to a ban on avoparcin in the European Union and a similarly acting product, virginiamycin, in Denmark (5).

Use of antibiotics in animals for therapeutic indications has also caused concern. A Food and Drug Administration expert panel has recommended caution in the approval of quinolones for use in animals because of the potential consequences for people. Use of fluoroquinolones, including enrofloxacin and danofloxacin, in animal husbandry has already led to antibiotic resistance among the zoonotic pathogens campylobacter and salmonella (7).
Thus, antibiotic resistance, which was initially a problem for hospitals and developing countries, now affects the world at large. Its control will require action that focuses not only on medical but on veterinary, agricultural and aquacultural use in order to minimize the environmental impact. Misuse of antibiotics for viral diseases should be addressed by education of consumers and prescribers. Furthermore, use in animals should be limited to treatment which does not perpetuate the selection of resistance. The smaller the extent of exposure to antibiotics, the less likely the selection and transfer of resistance traits among environmental bacteria and the lower the probability that a resistant pathogen will arise.

References


Future trends in biological standardization

The report of the WHO Expert Committee on Biological Standardization (ECBS), which held its 48th meeting in Geneva in October 1997, will shortly be published in the WHO Technical Report Series. The purpose of the ECBS is to review developments and recommend procedures to assure the quality, safety and efficacy of biological substances used in medicine. The increasing complexity and sophistication of these substances, as well as the rapid growth in their volume, present a considerable challenge for regulatory authorities, especially in the developing world.

Many of the items on the agenda of the ECBS meeting reflect the expanding capacity of biological technology and the increased diversity of new products. Some traditional substances have now been replaced by recombinant DNA products, and new diagnostic processes such as gene amplification techniques for virological safety testing of blood and blood products have been developed. New approaches to in-process testing procedures using molecular-based techniques are also set to reduce testing in animals. The complexity of available biological products underlines the importance of WHO as a source of expertise and a facilitator of the exchange of information worldwide.

During the meeting, the ECBS adopted guidelines for the production and quality control of synthetic peptide vaccines. Development of this kind of vaccine is still at an early stage and a flexible approach to control is needed. The importance of providing evidence of consistency from batch to batch based on physicochemical techniques is emphasized, but biological characterization will also play a critical role. Because synthetic peptide vaccines are not all produced in the same way, each vaccine will need to be given careful individual consideration of its specific features. Flexibility should be exercised in the application of the guidelines in order to reflect the intended clinical use.

Requirements for inactivated tick-borne encephalitis vaccine were also adopted by the ECBS. Tick-borne encephalitis is an acute viral infection caused by two closely-related viruses of the Flaviviridae family, and transmitted to man by ticks. The disease is endemic in forested areas of central Europe and in Asia, where vaccination is considered an important public health measure. The requirements have been formulated to take account of current manufacturing processes and controls and provide
for production of vaccine in chicken embryos or on continuous cell lines. The vaccines are prepared from harvested virus propagated on appropriate cells and this procedure is followed by inactivation, purification and formulation.

In addition, guidelines for thromboplastins and plasma used to control oral anticoagulant therapy were adopted. These represent the current state of the art. In producing the guidelines, major changes were made to the previous requirements established in 1983 following extensive consultation and discussions with international associations and experts.

The test for potency to be performed by manufacturers on recombinant hepatitis B vaccines was established in 1989. Since that time, in vitro potency tests based on ELISA have been developed. These assays are product specific and have been validated by demonstrating a correlation with mouse immunogenicity test results. An amendment to the requirements has thus been adopted by the ECBS to permit the use of in vitro tests validated by correlation with the immune response in humans or with results obtained in mouse immunogenicity tests.

The ECBS established new or replacement international reference materials and a number were discontinued. These are listed below. The Committee also considered other issues relevant to its work, in particular the establishment of an international working group for the standardization and control of nucleic acid vaccines. This is an important and complex area regarding testing and control procedures and requires guidance on the preparation and quality control of plasmid DNA vaccines now entering clinical trials.

<table>
<thead>
<tr>
<th>International biological standards and reference reagents established by the 48th WHO Expert Committee on Biological Standardization, 1997</th>
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<tr>
<td><strong>Antibodies</strong></td>
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<tr>
<td>antihuman platelet</td>
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<td>stem cell factor</td>
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<td>FMS-like tyrosine kinase 3 ligand</td>
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<td>platelet derived growth factor</td>
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<td>low virus reference for MAPREC analysis of polio virus type 3 (Sabin)</td>
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<tr>
<td>high virus reference for MAPREC analysis of poliovirus type 3 (Sabin)</td>
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<td><strong>Discontinuations</strong></td>
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<td>diphtheria toxoid (plain)</td>
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<td>lecithin (egg)</td>
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<td>poliomyelitis vaccine (inactivated)</td>
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<td>tetanus toxoid</td>
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<tr>
<td>swine erysipelas vaccine</td>
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Regulatory Matters

Mibefradil: harmful interactions

The new selective calcium channel blocker, mibe-
fradil, which is indicated for hypertension and
chronic stable angina, has been voluntarily with-
drawn from the market by the manufacturer as a
result of new information about potentially harmful
interactions with other drugs, making safe use of
the drug too complex (1, 2).

As reported previously (3), mibefradil interacts
dangerously with many commonly prescribed
cardiovascular drugs. Principally, it inhibits the
activity of certain liver enzymes which are important
for drug elimination, resulting in an accumulation at
dangerous levels.

More than 25 drugs are presently known to be
potentially dangerous if used with mibefradil and,
since the drug has not been shown to offer benefits
over and above those of drugs in the same therapeu-
tic group which are currently marketed, its use
is considered to be an unreasonable risk to con-
sumers (1). Patients taking mibefradil are advised
not to discontinue treatment, but to consult a physi-
cian about appropriate alternative therapy.

References:

1. Dear Doctor letter from Roche Laboratories Inc. dated
June 8 1998 and circulated under cover of FDA Talk
Paper T98-33, 1998
2. Dear Doctor letter from Roche Products Ltd. dated 8
June 1998 and circulated by Medicines Control Agency on

HIV vaccine trial approved

United States of America — The Food and Drug
Administration has given an FDA investigational
new drug approval for the first phase III clinical trial
of a candidate HIV-1 vaccine (1, 2).

The trial will be a placebo controlled study of 5000
healthy volunteers who have tested negative for
HIV, but are at high risk of contracting the disease.
Approval has also been requested for a similar trial
to be carried out in 2500 injecting drug users in
Thailand (3).

The vaccine is composed of recombinant gp120
envelope antigens from two HIV-1 strains. In earlier
phase I and II trials carried out in some 1200 peo-
ple, the vaccine induced a strong circulating anti-
body response in 99% of subjects. The present
phase III trials are meant to demonstrate whether
and to what extent these antibodies protect against
HIV (4).

References

1. Letter dated 2 July 1998 to WHO from the Office of
Vaccines Research and Review, Center for Biologics
Evaluation and Research, Food and Drug Administration,
United States of America.
2. Communication to UNAIDS from Don Francis, VaxGen,
3. Approval given for trials of AIDS vaccine. British
4. 1. HIV-1 vaccine trial go-ahead reawakens ethics

Counterfeiting: halothane
replaced by chloroform

Pakistan — The provincial drug testing laboratory
in Peshawar has detected a counterfeit product
labelled as a general anaesthetic containing hal-
thane. However, the genuine active ingredient has
been replaced with chloroform, a hepatotoxic
compound. The counterfeit product, which is
claimed to be produced by Zeneca in the United
Kingdom, was purchased in a local market but is
also believed to be supplied to a number of private
and public hospitals.


Warfarin interaction with
miconazole oral gel

Australia — The Adverse Drug Reaction Advisory
Committee has received 11 reports documenting an
interaction between warfarin and miconazole oral gel. Antifungal agents are known to inhibit cytochrome P450 enzymes and potentiate the anticoagulant effect of warfarin. The international normalized ratio (INR) in some cases was elevated to as high as 15.6. Five cases were symptomless, but 6 patients developed bruising, haematuria or mucocutaneous bleeding.

Since miconazole oral gel is applied topically, it is presumed that absorption is limited. However, systemic absorption is possible through inflamed mucosa and ingestion from the gastrointestinal tract.

In many countries miconazole oral gel is available without prescription and warfarin patients will need to be warned of this interaction.


Nandrolone-containing products withdrawn

France — All medical products containing the anabolic steroid, nandrolone, have been withdrawn from the market following a re-evaluation of the clinical data supporting efficacy. These products were indicated for malnutrition in the elderly, postsurgical treatment and for major burns. One eye-drip formulation remains on the market.


Sibutramine scheduled as a controlled substance

United States of America — In November 1997, sibutramine was approved by the Food and Drug Administration as an oral anorectic for the long-term management of obesity.

Sibutramine produces central nervous stimulation and amphetamine effects in humans. It has now been placed under schedule IV of the Controlled Substances Act since it is considered as having a low abuse potential which may lead to limited physical and psychological dependence.


Bromfenac withdrawal

United States of America — In July 1997, the Food and Drug Administration approved bromfenac, a nonsteroidal anti-inflammatory drug, for the short-term management of pain. Following reports of severe liver failure requiring transplantation, the labelled warning was reinforced by the manufacturer in February 1998 (1).

It has now been decided to withdraw the product as a result of 4 deaths, 8 cases of liver transplantation and 12 reports of liver damage. In patients who have taken the drug for longer than the recommended 10 days, it has been estimated that severe liver injury occurs in 1 in every 10 000–20 000 people. Given the availability of other therapies, it was not considered practical to implement the restrictions necessary to ensure safe use of less than 10 days.

References

Discontinuation of international antibiotic reference preparations

World Health Organization — The WHO Expert Committee on Biological Standardization has discontinued the international reference preparations for a number of antibiotics because requirements in major pharmacopoeias no longer impose a microbiological assay. The antibiotics in question are doxycycline, demecycline (demethylchlorotetracycline), minocycline, oxytetracycline, and tetracycline.

It should be noted that discontinuation of the international reference preparation for these antibiotics will automatically mean discontinuation of the international unit (IU) for these substances.


Seratrodast and hepatic dysfunction

Japan — The Ministry of Health and Welfare has issued a warning regarding hepatic dysfunction
associated with the use of seratrodast, for the
treatment of bronchial asthma. Hepatic dysfunction
was reported in 49 patients, of whom 4 died from
fulminant hepatitis. The product information has
been amended to advise that liver function tests
should be performed periodically. In the event of
abnormal tests, treatment should be interrupted.

Reference: Pharma Japan, Number 11594, April 1998.

Meloxicam safety similar to other NSAIDs

Sweden — The Medical Products Agency has
analysed reports of adverse drug reactions re-
ceived for meloxicam, a cyclooxygenase (COX-2)
inhibitor that has been claimed to cause less gas-
trintestinal reactions than other NSAIDs.

During the first year of marketing, 15 adverse
reactions have been reported. Of these, 5 cases
were for skin reactions and 6 of gastrointestinal
disturbances. Although use of the drug has been
limited, these reports suggest that meloxicam may
have a similar safety profile to other NSAIDs.


Proxibarbal withdrawn from the market

France — The barbiturate, proxibarbal, which has
been marketed since 1977 has been re-evaluated
by the Adverse Drug Reactions Board of the Medi-
cines Agency. In carrying out the review it was
concluded that proxibarbal may induce
immunoallergenic thrombopenia with potentially
severe health consequences. The marketing au-
thorization has consequently been suspended and
the manufacturer has withdrawn the product from
the market. Proxibarbal is still available in Hungary
and Poland.

Reference: Communication to WHO from the Agence du
Médicament, April 1998.

Cholestin an unapproved drug

United States of America — The Food and Drug
Administration has determined that cholestin, a
product marketed as a dietary supplement intended
to affect cholesterol levels, is an unapproved drug.
Cholestin is derived from yeast grown on red rice
but also contains lovastatin and unsaturated fatty
acids.

Since November 1997, the Food and Drug Adminis-
tration has made an extensive review to determine
whether to regulate cholestin. Lovastatin is the
active ingredient of an already marketed prescrip-
tion drug to lower cholesterol levels. It was there-
fore considered that cholestin cannot be considered
purely as a food supplement (1).

Meanwhile, the company has contested the deci-
sion and will be allowed to continue marketing
during the appeal period. When a final decision on
this case has been reached, a clearer definition of
the regulatory status of drugs, dietary supplements
and food will have been established (2).

References
2. SCRIP, No. 2348, 1 July 1998.

Vigabatrin and visual defects

Vigabatrin is indicated for the treatment of epilepsy
not satisfactorily controlled by other drugs and as
monotherapy for infantile spasms. The Committee
on Safety of Medicines has reminded physicians
that since 1989, 41 reports of visual field defects
have been received in connection with this product
(1). Epidemiological studies suggest that 15 out of
10 000 patients treated yearly within Europe experi-
ence symptoms of visual field defects (2). Onset
can vary from one month to several years after
taking vigabatrin.

Patients should be warned to report any new visual
symptoms and they must be referred to an ophthal-
moscopy if this occurs.

References
## ATC/DDD Classification (final)

The following final classifications were agreed at a meeting of the WHO International Drug Utilization Working Group which took place from 27–28 October 1997 in Oslo. They came into force on **30 April 1998**. All requests for classification should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, P.O. Box 100, Velvet, 0518, Oslo, Norway (telephone: 00 47 22 16 9811, fax: 0047 22 16 9818, e-mail: whocc@nmd.no). The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

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

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### New ATC 5th level codes:

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<td>tolterodine</td>
</tr>
<tr>
<td>L02B G05</td>
<td>vorozole</td>
</tr>
</tbody>
</table>

### Change of name:

- **previous**: (cytokines)
- **new**: colony stimulating factor
### ATC code changes:

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>previous Code</th>
<th>new Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>apomorphine</td>
<td>V03A B07</td>
<td>N04B C07</td>
</tr>
<tr>
<td>didanosine</td>
<td>J05A B07</td>
<td>J05A F02</td>
</tr>
<tr>
<td>interferon alfa</td>
<td>L03A A04</td>
<td>L03A B01</td>
</tr>
<tr>
<td>interferon beta</td>
<td>L03A A11</td>
<td>L03A B02</td>
</tr>
<tr>
<td>interferon gamma</td>
<td>L03A A08</td>
<td>L03A B03</td>
</tr>
<tr>
<td>interleukin-2</td>
<td>L03A A01</td>
<td>L03A C01</td>
</tr>
<tr>
<td>lamivudine</td>
<td>J05A B10</td>
<td>J05A F05</td>
</tr>
<tr>
<td>milnacipran</td>
<td>N06A A24</td>
<td>N06A X17</td>
</tr>
<tr>
<td>nevirapine</td>
<td>J05A X03</td>
<td>J05A G01</td>
</tr>
<tr>
<td>poly I:C</td>
<td>L03A A05</td>
<td>L03A X07</td>
</tr>
<tr>
<td>poly ICLC</td>
<td>L03A A06</td>
<td>L03A X08</td>
</tr>
<tr>
<td>stavudine</td>
<td>J05A X04</td>
<td>J05A F04</td>
</tr>
<tr>
<td>terazosin</td>
<td>C02C A05</td>
<td>G04C A03</td>
</tr>
<tr>
<td>thymopentin</td>
<td>L03A A07</td>
<td>L03A X09</td>
</tr>
<tr>
<td>trimetazidine</td>
<td>C01D X17</td>
<td>C01E B14</td>
</tr>
<tr>
<td>venlafaxine</td>
<td>N06A A22</td>
<td>N06A X16</td>
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<tr>
<td>zalcitabine</td>
<td>J05A B08</td>
<td>J05A F03</td>
</tr>
<tr>
<td>zidovudine</td>
<td>J05A B05</td>
<td>J05A F01</td>
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</table>

### 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>atorvastatin</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>C10A A05</td>
</tr>
<tr>
<td>azathioprine</td>
<td>0.15</td>
<td>g</td>
<td>O, P</td>
<td>L04A X01</td>
</tr>
<tr>
<td>cerivastatin</td>
<td>0.2</td>
<td>mg</td>
<td>O</td>
<td>C10A A06</td>
</tr>
<tr>
<td>ciclosporin</td>
<td>0.25</td>
<td>g</td>
<td>O, P</td>
<td>L04A A01</td>
</tr>
<tr>
<td>dolasetron</td>
<td>0.2</td>
<td>g</td>
<td>O</td>
<td>A04A A04</td>
</tr>
<tr>
<td>donepezil</td>
<td>7.5</td>
<td>mg</td>
<td>O</td>
<td>N07A A05</td>
</tr>
<tr>
<td>estradiol</td>
<td>1</td>
<td>mg</td>
<td>TD gel</td>
<td>G03C A03</td>
</tr>
<tr>
<td>etonogestrel</td>
<td>67</td>
<td>µg</td>
<td>SC implant</td>
<td>G03A C08</td>
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<tr>
<td>ginkgo biloba</td>
<td>0.12</td>
<td>g</td>
<td>O</td>
<td>N06B X19</td>
</tr>
<tr>
<td>indinavir</td>
<td>2.4</td>
<td>g</td>
<td>O</td>
<td>J05A E02</td>
</tr>
<tr>
<td>lercanidipine</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>C08C A13</td>
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<td>mibefradil</td>
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<td>O</td>
<td>C08C X01</td>
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<td>mizolastine</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>R06A X25</td>
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<tr>
<td>muromonab-CD3</td>
<td>5</td>
<td>mg</td>
<td>P</td>
<td>L04A A02</td>
</tr>
<tr>
<td>mycophenolic acid</td>
<td>2</td>
<td>g</td>
<td>O</td>
<td>L04A A06</td>
</tr>
<tr>
<td>naratriptan</td>
<td>2.5</td>
<td>mg</td>
<td>O</td>
<td>N02C C02</td>
</tr>
<tr>
<td>ritonavir</td>
<td>1.2</td>
<td>g</td>
<td>O</td>
<td>J05A E03</td>
</tr>
<tr>
<td>stavudine</td>
<td>80</td>
<td>mg</td>
<td>O</td>
<td>J05A F04</td>
</tr>
<tr>
<td>tacrolimus</td>
<td>5</td>
<td>mg</td>
<td>O, P</td>
<td>L04A A05</td>
</tr>
<tr>
<td>tiagabine</td>
<td>30</td>
<td>mg</td>
<td>O</td>
<td>N03A G06</td>
</tr>
</tbody>
</table>

### Change of DDD:

- etidronic acid (based on treatment of osteoporosis) 0.4 g O M05B A01
- topiramate (based on combination therapy) 0.3 g O N03A X11
- zidovudine (based on combination therapy) 0.6 g O, P J05A F01
# ATC/DDD Classification (temporary)

The following temporary classifications were agreed at a meeting of the WHO International Drug Utilization Working Group which took place on 30 and 31 March 1998 in Oslo. Comments on, or objections to, the classification should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, P.O. Box 100, Veivet, 0518, Oslo, Norway (telephone: 00 47 22 16 9811, fax: 0047 22 16 9818, e-mail: whocc@nmd.no) before 15 November 1998. Provided there have been no objections, the classification will come into force on 31 December 1998. A final list of classifications will be published subsequently in this journal. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

## ATC Level codes

<table>
<thead>
<tr>
<th>ATC Level codes (other than 5th level):</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Helicobacter pylori</em>, combinations for eradication of</td>
</tr>
<tr>
<td>Antipsoriatrics, other, for systemic use</td>
</tr>
<tr>
<td>Gynecologicals, other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATC Level codes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>azidamfenicol</td>
</tr>
<tr>
<td>albumin tannate, combinations</td>
</tr>
<tr>
<td>balsalazide</td>
</tr>
<tr>
<td>benzoyl peroxide, combinations</td>
</tr>
<tr>
<td>brimonidine</td>
</tr>
<tr>
<td>candesartan</td>
</tr>
<tr>
<td>candesartan with a diuretic</td>
</tr>
<tr>
<td>canrenone</td>
</tr>
<tr>
<td>carbamide, combinations</td>
</tr>
<tr>
<td>charcoal, medicinal, combinations</td>
</tr>
<tr>
<td>cefdinir</td>
</tr>
<tr>
<td>cefprozil</td>
</tr>
<tr>
<td>cinolazepam</td>
</tr>
<tr>
<td>delavirdine</td>
</tr>
<tr>
<td>diphtheria-<code>haemophilus influenzae</code> B- pertussis-poliomyelitis-tetanus</td>
</tr>
<tr>
<td>efavirenz</td>
</tr>
<tr>
<td>emedastine</td>
</tr>
<tr>
<td>ethambutol, combinations</td>
</tr>
<tr>
<td>etilefrine, combinations</td>
</tr>
<tr>
<td>ferric ammonium citrate</td>
</tr>
<tr>
<td>ferric oxide dextran complex</td>
</tr>
<tr>
<td>ferric proteinsuccinylate</td>
</tr>
<tr>
<td>fluocinonide with an antibacterial fumaric acid derivatives, combinations</td>
</tr>
<tr>
<td>gadoversetamide</td>
</tr>
<tr>
<td>heparin</td>
</tr>
<tr>
<td>hexamidine</td>
</tr>
<tr>
<td>hydrocortisone, combinations</td>
</tr>
<tr>
<td>hydroxocobalamin, combinations</td>
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### New ATC 5th level codes (continued):

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>ibopamine</td>
<td>S01F B03</td>
</tr>
<tr>
<td>imiquimod</td>
<td>D06B B10</td>
</tr>
<tr>
<td>immunocyanin</td>
<td>L03A X10</td>
</tr>
<tr>
<td>isoprenaline, combinations</td>
<td>R03C B51</td>
</tr>
<tr>
<td>isopropanol</td>
<td>D08A X05</td>
</tr>
<tr>
<td>kanamycin</td>
<td>S01A A24</td>
</tr>
<tr>
<td>S-ketamine</td>
<td>N01A X14</td>
</tr>
<tr>
<td>levobupivacaine</td>
<td>N01B B10</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>J01M A12</td>
</tr>
<tr>
<td>macrogol, combinations</td>
<td>A06A D65</td>
</tr>
<tr>
<td>melitracen with a psycholeptic</td>
<td>N06C A02</td>
</tr>
<tr>
<td>memantine</td>
<td>N06B X21</td>
</tr>
<tr>
<td>mometasone</td>
<td>R01A D09</td>
</tr>
<tr>
<td>nystatin, combinations</td>
<td>G01A A51</td>
</tr>
<tr>
<td>omeprazole, amoxicillin, and metronidazole, combinations</td>
<td>A02B D01</td>
</tr>
<tr>
<td>oprelvekin</td>
<td>L03A C02</td>
</tr>
<tr>
<td>penciclovir</td>
<td>J05A B13</td>
</tr>
<tr>
<td>phenylephrine, combinations</td>
<td>R01B A53</td>
</tr>
<tr>
<td>propanol, combinations</td>
<td>D08A X53</td>
</tr>
<tr>
<td>propentofylline</td>
<td>N06B C02</td>
</tr>
<tr>
<td>quetiapine</td>
<td>N05A H04</td>
</tr>
<tr>
<td>ramipril with a calcium channel blocker</td>
<td>C09B B05</td>
</tr>
<tr>
<td>reboxetine</td>
<td>N06A X18</td>
</tr>
<tr>
<td>rivastigmine</td>
<td>N07A A06</td>
</tr>
<tr>
<td>salicylic acid</td>
<td>S01B C08</td>
</tr>
<tr>
<td>salmeterol with an anti-asthmatic</td>
<td>R03A K06</td>
</tr>
<tr>
<td>sibutramine</td>
<td>A08A A10</td>
</tr>
<tr>
<td>sildenafil</td>
<td>G04B E03</td>
</tr>
<tr>
<td>tazarotene</td>
<td>D05A X05</td>
</tr>
<tr>
<td>tretinoin, combinations</td>
<td>D10A D51</td>
</tr>
<tr>
<td>triamcinolone</td>
<td>R01A D11</td>
</tr>
<tr>
<td>zaleplon</td>
<td>N05CF03</td>
</tr>
<tr>
<td>combinations</td>
<td>A07BC30</td>
</tr>
<tr>
<td>combinations</td>
<td>S02DA30</td>
</tr>
</tbody>
</table>

#### Change of ATC code:

- **Previous:** zolpidem  
- **New:**  
  - zolpidem  
  - ATC code: N05CF02

#### Deleted ATC level:

- **Imidazopyrridines**  
  - ATC code: N05CG

#### Change of level name:

- **Previous:** cyclopyrrolones  
- **New:** benzodiazepine-related drugs  
  - ATC code: N05CF

- **Previous:** diazepines and oxazepines  
- **New:** diazepines, oxazepines and thiazepines  
  - ATC code: N05AH

- **Previous:** ferric oxide polymaltose complex  
- **New:** dextriferron  
  - ATC code: B03AB05
## 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>brimonidine</td>
<td>0.2</td>
<td>ml</td>
<td></td>
<td>S01EA05*</td>
</tr>
<tr>
<td>candesartan</td>
<td>8</td>
<td>mg</td>
<td>O</td>
<td>C09CA06*</td>
</tr>
<tr>
<td>cefdinir</td>
<td>0.6</td>
<td>g</td>
<td>O</td>
<td>J01DA42*</td>
</tr>
<tr>
<td>cidofovir</td>
<td>25</td>
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<td>P</td>
<td>J05AB12</td>
</tr>
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<td>eprosartan</td>
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<td>g</td>
<td>O</td>
<td>C09CA02</td>
</tr>
<tr>
<td>fentanyl beta</td>
<td>75</td>
<td>IU</td>
<td>P</td>
<td>G03GA06</td>
</tr>
<tr>
<td>grepafloxacin</td>
<td>0.4</td>
<td>g</td>
<td>O</td>
<td>J01MA11</td>
</tr>
<tr>
<td>irbesartan</td>
<td>0.15</td>
<td>g</td>
<td>O</td>
<td>C09CA04</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>0.25</td>
<td>g</td>
<td>O, P</td>
<td>J01MA12*</td>
</tr>
<tr>
<td>montelukast</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>R03DC03</td>
</tr>
<tr>
<td>pilocarpine</td>
<td>15</td>
<td>mg</td>
<td>O</td>
<td>N07AX01</td>
</tr>
<tr>
<td>polycarbophil calcium</td>
<td>2.5</td>
<td>g</td>
<td>O</td>
<td>A06AC08</td>
</tr>
<tr>
<td>reboxetine</td>
<td>8</td>
<td>mg</td>
<td>O</td>
<td>N06AX18*</td>
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<td>saquinavir</td>
<td>1.8</td>
<td>g</td>
<td>O</td>
<td>J05AE01</td>
</tr>
<tr>
<td>tolcapone</td>
<td>0.45</td>
<td>g</td>
<td>O</td>
<td>N04BX01</td>
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<tr>
<td>tolterodine</td>
<td>4</td>
<td>mg</td>
<td>O</td>
<td>G04BD07</td>
</tr>
<tr>
<td>zolmitriptan</td>
<td>2.5</td>
<td>mg</td>
<td>O</td>
<td>N02CC03</td>
</tr>
</tbody>
</table>

* temporary ATC code
Essential Drugs

WHO Model Formulary

As described in previous issues of this journal, work is now under way on the WHO Model Formulary, and draft texts will be published regularly to obtain comments on the material proposed for publication. Observations concerning the following sections should be addressed to: Drug Selection and Information (DSI), Division of Drug Management & Policies, World Health Organization, 1211 Geneva 27, Switzerland.

Immunosuppressives, anti-neoplasics and drugs used in palliative care

Immunosuppressive drugs

Immunosuppressive drugs are administered to recipients of tissue or organ transplants to suppress the rejection mechanism, or as a second-line drug in rheumatology and dermatology. Because immunosuppressives are non-specific in their action, careful monitoring of the peripheral blood count is required, with dose adjustments to prevent bone-marrow toxicity. Patients receiving these drugs are particularly prone to atypical infections. Treatment should only be initiated by a specialist.

Azathioprine is the most widely used drug for transplant recipients. It is useful when corticosteroid therapy alone has proven inadequate or for other conditions when a reduction in the dosage of concurrently administered corticosteroids is required. It is metabolized to mercaptopurine and doses therefore need to be reduced when this drug is used concurrently with allopurinol. The predominant toxic effect is myelosuppression, although hepatic toxicity is also a known reaction.

Azathioprine is a potent immunosuppressant which is virtually free of myelotoxic effects, but is markedly nephrotoxic. It is particularly useful for prevention of graft rejection or graft-versus-host disease. The dose is adjusted by monitoring blood-ciclosporin concentrations (trough concentration) and renal function. Dose-related increases in serum creatinine and blood urea nitrogen (BUN) during the first few weeks may necessitate dose reduction.

Corticosteroids such as prednisolone have significant immunosuppressant activity and can also be used to prevent rejection of organ transplants.

AZATHIOPRINE
Tablet: 50 mg
Powder for injection: 100 mg (as sodium salt) in vial

Uses: As an adjunct to prevent rejection in transplant recipients and as a disease-modifying agent in other conditions in which corticosteroids are the primary treatment, in order to reduce their use.

Dosage:
3 mg/kg/day 1–3 days prior to surgery and at the time of surgery. 1–2 mg/kg single daily dose as maintenance therapy. Reduce the dose in the event of renal or hepatic impairment and in elderly patients.

Contraindications: Hypersensitivity to azathioprine and mercaptopurine.

Precautions: Weekly blood counts necessary for the first 8 weeks of treatment and every 3 months thereafter.

Adverse effects: Hypersensitivity reactions, malaise, dizziness, vomiting, fever, muscular pains, arthralgia, disturbed liver function, cholestatic jaundice, arrhythmia, hypotension or interstitial nephritis call for immediate withdrawal.

Haematological toxicity includes leukopenia and thrombocytopenia, which may be reversible upon withdrawal, and increased susceptibility to infections. Gastrointestinal disturbances include nausea, vomiting and hepatotoxicity.
**Drug interactions:** These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

**CICLOSPORIN**

*Capsule: 25 mg  
Concentrate for injection: 50 mg/ml in 1-ml ampoule*

**Uses:** In combination with corticosteroids, to prevent rejection of renal, hepatic and cardiac transplants. Treatment of chronic rejection in patients previously treated with other immuno-suppressants. Treatment of graft-versus-host disease after bone-marrow transplantation.

**Dosage:**

**Prevention of transplant rejection**

*Oral administration adults and children:* 12–15 mg/kg daily administered 4–12 hours prior to and for 1–2 weeks after surgery. 5–10 mg/kg daily thereafter.

*Intravenous infusion adults and children:* 2–6 mg/kg daily administered 4–12 hours prior to and following surgery until the patient can tolerate oral dosage forms. If necessary, one-third of the oral dose can be given by intravenous infusion over 2–6 hours.

When given concomitantly with other immuno-suppressants, lower dosages should be used.

**Prevention and treatment of graft-versus-host disease**

*Intravenous infusion adults and children:* 3–5 mg/kg daily over 2–6 hours beginning on the day before transplant surgery to 2 weeks after surgery.

*Oral administration adults and children:* 12.5 mg/kg orally for 3–6 months, with a gradual dosage reduction.

**Precautions:** Emergency care and facilities should be available in the event of adverse reactions to ciclosporin. Monitor renal and hepatic functions and blood pressure.

**Adverse effects:** Frequently, dose-related and reversible nephrotoxicity resulting in increases in serum creatinine and BUN unrelated to rejection, may require dosage adjustments. Electrolyte disturbances including hyperkalaemia, hepatic dysfunction, hypertension (especially in heart transplant patients), incidence of malignancies and lymphoproliferation disorders, increased susceptibility to infections due to immunosuppression, gynaecomaestia, gastrointestinal disturbances, gingival hyperplasia, allergic reactions, thrombocytopenia (sometimes with haemolytic uraemic syndrome) have been reported. Also, mild anaemia, tremors, convulsions, neuropathy, myopathy, or muscle weakness.

**Drug interactions:** These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

**Cytotoxic drugs**

The treatment of cancer with drugs, radiotherapy and surgery is complex and should only be undertaken by an oncologist. For this reason, the following information is provided merely as a guide and the products mentioned should only be administered by specialized medical personnel.

Chemotherapy may be curative, or used to alleviate symptoms, or to prolong life. Where the condition cannot be managed with cytotoxic drugs, alternative palliative treatment (see page 163) should be considered. For some tumours, single-agent chemotherapy may be adequate, but for many malignancies a combination of drugs provides the best response. Examples of combination therapy include:

- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) for non-Hodgkin disease.
- ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) for Hodgkin disease.
- MOPP (mustine, vincristine, procarbazine, prednisolone) also for Hodgkin disease.

Drug combinations are, however, more toxic than single agents. Cytotoxic drugs are often combined with other classes of drugs in the treatment of malignant conditions. Such drugs include hormone agonists and antagonists, corticosteroids and immunostimulant drugs. The following information covers drugs that have specific antitumour activity. However, they are toxic and should be used with great care and monitoring. The specific doses for cytotoxic drugs have been omitted from this section since treatment should be undertaken by specialists using agreed regimens. Health authorities may wish to formulate their own regimens on the basis of expert advice.

**Precautions:** Treatment with cytotoxic drugs should be initiated only after baseline tests of liver
and kidney function have been performed and blood counts established. As a result of these tests, it may be necessary to modify or delay treatment in certain circumstances. The patient should also be monitored regularly during chemotherapy and cytotoxic drugs withheld if there is significant deterioration in bone-marrow, liver or kidney function. Doses should be calculated carefully with regard to individual variation of drug metabolism, particularly fluorouracil and mercaptopurine. This variation can make a considerable difference to the dosage requirements. Many cytotoxic drugs are teratogenic and should not be administered during pregnancy, especially in the first trimester. Contraceptive measures are required both during therapy and for some time afterwards. Cytotoxic drugs should be administered in such a way as to avoid undue toxicity to the patient or exposure during handling by the health care provider.

**Adverse effects:** Cytotoxic drugs have a considerable potential to damage normal tissue. Specific adverse effects apply, but a number of effects are common to all cytotoxics such as bone-marrow and immunological suppression. Furthermore, the concomitant use of immunosuppressive drugs will enhance susceptibility to infections. Fever associated with neutropenia or immunosuppression requires immediate treatment with antibiotics. Nausea and vomiting following administration of cytotoxic drugs and abdominal radiotherapy are often distressing and could compromise further treatment. Nausea and vomiting may occur within 24 hours of cytotoxic treatment or later. In some cases, anticipatory nausea and vomiting occur prior to the next dose of treatment and can be managed by administering an appropriate anti-emetic.

Hyperuricaemia may complicate treatment of conditions such as non-Hodgkin lymphoma and leukaemia. Renal damage may result from the formation of uric acid crystals. Patients should be adequately hydrated, and hyperuricaemia can be managed with allopurinol initiated 24 hours before treatment and continued for 7–10 days afterwards. Alopecia is common during treatment with cytotoxic drugs. There is no treatment, but the condition often reverses spontaneously once treatment has stopped.

Extravasation of intravenously administered cytotoxic drugs can result in severe pain and necrosis of surrounding tissue. If extravasation occurs, the affected limb should be elevated and treated with cold compresses until the inflammation subsides. In severe cases, hydrocortisone cream may be applied topically to the site of inflammation.

**Alkylating agents** are among the most widely used drugs in cancer chemotherapy. They act by damaging DNA and therefore interfering with cell replication. However, there are two complications. Firstly, they affect gametogenesis and may cause permanent male sterility; in women, the reproductive span may be shortened by the onset of premature menopause. Secondly, they are associated with a marked increase in the incidence of acute non-lymphocytic leukaemia, in particular when combined with extensive radiation therapy.

Cyclophosphamide is one of many alkylating agents used in cancer therapy. It has the advantage of requiring hepatic activation before it is functional: it can therefore be given orally and is not a vesicant when given intravenously. Like all alkylating agents, its major toxic effects are myelosuppression, alopecia, nausea and vomiting. It can also cause haemorrhagic cystitis.

Cyclophosphamide is used either as part of curative treatment or as an adjuvant in non-Hodgkin lymphoma, breast cancer, childhood leukaemia, and ovarian cancer. It is also employed in several palliative regimens.

Chlormethine (mustine) is an alkylating agent which interferes with DNA replication and RNA transcription thereby disrupting nucleic acid function. It is part of the MOPP regimen used in the treatment of advanced Hodgkin disease and malignant lymphomas. Its toxicity causes myelosuppression, nausea, vomiting, alopecia and phlebitis.

**Cytotoxic antibiotics** are widely used in cancer chemotherapy. Simultaneous use of radiotherapy should be avoided since this may result in markedly enhanced toxicity to normal tissue.

Bleomycin is a unique antitumour antibiotic which causes DNA strand cleavage. However, it has several antineoplastic drug toxicities: it is known to cause a dose-related pneumonitis which can be fatal, and it is associated with rare acute hypersensitivity reactions. Cutaneous toxicity has also been reported. Bleomycin is a component of curative regimens for Hodgkin disease (ABVD) and testicular cancer (bleomycin, etoposide and cisplatin).

Dactinomycin is also an antineoplastic antibiotic. Its mechanism of action is not fully understood but it is
thought to inhibit DNA-dependent RNA synthesis by intercalating with base pairs and inhibiting DNA template activity. It is used primarily to treat paediatric cancers. Its toxicity is similar to that of doxorubicin, except for cardiotoxicity.

Doxorubicin is the most widely used anthracycline antineoplastic. It is incorporated into DNA and may cause cellular damage by a variety of mechanisms, the most important of which is now thought to be inhibition of topoisomerase II. Its primary toxic effects are myelosuppression, alopecia, nausea, vomiting, and dose-related cardiac dysfunction. It is also a vesicant and can cause severe skin ulceration with extravasation. Doxorubicin is used for acute leukaemias although other anthracyclines are more commonly used in these circumstances. Doxorubicin also plays a palliative role in the treatment of other malignancies.

**Antimetabolites** are incorporated into new nuclear material or combine irreversibly with vital cellular enzymes, thereby preventing normal cell division.

Cytarabine inhibits DNA metabolism by several mechanisms. Its effects are highly dependent upon the schedule of administration. It can cause myelosuppression, mucositis and, in high doses, central neurotoxicity. Its almost exclusive role is in the treatment of acute leukaemia, primarily in adults.

Fluorouracil is an antimetabolite which affects DNA and RNA metabolism. In addition, its site of action appears to be modified by the administration of other drugs, such as folinic acid, and by the method of administration, whether by bolus injection or by continuous infusion.

Fluorouracil causes myelosuppression but only minimal nausea and vomiting. When its action is modified by other drugs, its toxicity profile can change and mucositis and diarrhoea become important problems. Central neurotoxicity can also occur. Fluorouracil is primarily used in the adjuvant treatment of colorectal and breast cancer. It is also employed in the palliative treatment of other malignancies.

Mercaptopurine is an antimetabolite whose mechanism of action is unclear. It can be administered orally and myelosuppression and nausea are the only important toxic effects. It is frequently used in the therapy of childhood leukaemia.

Another antimetabolite, methotrexate, acts by interfering with folic acid metabolism. Like fluorouracil it is myelotoxic, but nausea and vomiting are minimal. It also causes mucositis. Renal impairment reduces methotrexate excretion and can exacerbate toxicity. Methotrexate has been used for many years to treat a variety of malignancies and was the first cytotoxic to cure a solid tumour (choriocarcinoma). Currently, it plays a major role as an adjuvant for the therapy of breast cancer.

Calcium folinate is used to counteract the folate antagonist action of methotrexate and thus speed recovery from methotrexate-induced mucositis or myelosuppression. Calcium folinate also interacts with fluorouracil and an enhanced effect has been demonstrated when the two are used together for metastatic colonic cancer.

**The vinca alkaloids**, vinblastine and vincristine, are primarily used in the treatment of haematologic malignancies, although vinblastine is a component of some regimens used for solid tumours and they act by disrupting the mitotic spindle. They can cause neurotoxicity, although this is much more of a clinical problem with vincristine. Myelosuppression is more common with vinblastine.

Vincristine is part of the CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen used in the management of non-Hodgkin lymphoma. It is also employed in the therapy of acute childhood lymphocytic leukaemia. The most important use of vinblastine is as one of the agents in the ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regimen for Hodgkin disease.

Etoposide is one of the two epipodophyllotoxins used in cancer therapy. It is thought to inhibit topoisomerase II. Like other antineoplastics, it causes myelosuppression and alopecia, and it can cause hypotension during infusion. It does not produce significant nausea and vomiting. Etoposide is an important component of the curative therapy of testicular carcinoma and is used in several regimens for non-small-cell and small-cell lung cancers.

The only enzyme used in cancer therapy, asparaginase depletes cellular stores of asparagine thus disrupting protein synthesis. Its toxicity profile is broad and the drug must be carefully administered. It is an important component in the management of childhood leukaemia, but is not used in any other malignancy.

A simple metal-containing compound, cisplatin, is thought to act by covalent binding to DNA. It is only
mildly myelosuppressive and produces slight alopecia. However, it causes severe, dose-related nausea and vomiting. It is also nephrotoxic and neurotoxic. Nephrotoxicity can be reduced by maintaining high urine output during cisplatin administration and immediately afterwards, but neurotoxicity is often dose-limiting. Cisplatin is of primary importance in the treatment of ovarian and testicular malignancies. It is also a component of regimens used in non-small-cell and small-cell lung cancer and plays a palliative role in other malignancies.

Dacarbazine is a unique agent which, although developed as an antimetabolite, is thought to act as an alkylating agent. Its major toxic effects are myelosuppression, nausea and vomiting. It is a primary component of the ABVD regimen for Hodgkin disease. It is also used in the palliative therapy of malignant melanoma.

Levamisole is an anthelminthic with immunostimulating properties. In doses used in humans, its major toxic effects are a variety of CNS symptoms, nausea, and dermatitis. It is used in combination with fluorouracil as adjuvant therapy for colorectal cancer. Its mode of action in that combination is unknown.

Procarbazine is thought to inhibit protein, DNA and RNA synthesis. It is used in the treatment of advanced Hodgkin disease. It is often used in combination with chloroethamine, vincristine and prednisolone (MOPP regimen). Toxic effects include myelosuppression, nausea, vomiting, CNS symptoms and depression. Procarbazine possesses a weak monoamine oxidase inhibitory effect.

**ASPARAGINASE**  
*Powder for injection: 10 000 IU in vial*  
**Uses:** Acute lymphocytic leukaemia.  
**Contraindications:** Hypersensitivity.  
**Precautions:** Because of the possibility of hypersensitivity reactions, resuscitation equipment and treatment should be readily available. Hepatic, renal and pancreatic function, blood counts, and blood glucose concentration should be determined before, and periodically after, therapy.  
**Adverse effects:** Allergic reactions are sometimes severe and include elevation of liver enzymes, hypofibrinogenaemia, leukopenia, prerenal azotemia with increased calcium and phosphorus excretion. Rarely, transient proteinuria, acute renal failure and fatal renal insufficiency have occurred. Impairment of pancreatic function, fatal acute haemorrhagic hepatitis, hyperosmolar, non-ketotic hyperglycaemia with glycosuria and polyuria which may be reversible upon withdrawal, have also been reported. CNS effects include EEG changes, depression, hyperexcitability, somnolence, lethargy, fatigue, convulsions, hallucinations and, rarely, Parkinson-like syndrome, or acute organic brain syndrome similar to acute alcoholic delirium tremens. Nausea, vomiting, abdominal cramps, anorexia, diarrhoea, stomatitis, intestinal ulcers and fatal hyperthermia have also been reported.

**BLEOMYCIN**  
*Powder for injection: 15 IU (sulfate) in vial*  
**Uses:** As an adjunct to surgery and radiation therapy in the palliative treatment of Hodgkin and non-Hodgkin lymphomas including reticulum cell sarcoma and lymphosarcoma, carcinomas of the head, neck, larynx, cervix, penis, skin, vulva, testicles and including embryonal cell carcinoma, choriocarcinoma and teratocarcinoma.  
**Contraindications:** Hypersensitivity.  
**Precautions:** Patients should be monitored and if signs of pulmonary toxicity appear the drug should be withdrawn. Auscultation of the lungs and a chest X-ray are recommended before and at periodic intervals during therapy.  
**Adverse effects:** Pneumonitis may progress to pulmonary fibrosis, especially at cumulative doses greater than 300 units and in the elderly. Mucositis, including stomatitis and dermatological effects, hypeaesthesia followed by hyperaesthesia, urticaria, ichthyosis, or rashes frequently occur. Myocardial infarction, thrombotic microangiopathy or cerebral arteritis, Raynaud syndrome, fever and chills following injection, thrombocytopenia, leukopenia, slight haemoglobinaemia, nausea, vomiting, fatigue, hypotension and phlebitis are rarely reported. Early hypersensitivity reactions may also occur.

**CALCIUM FOLINATE**  
*Tablet: 15 mg*  
*Injection: 3 mg/ml in 10-ml ampoule*  
**Uses:** Used routinely in high-dose methotrexate therapy, it is usually given 24 hours after metho-
trexate. It is also used to treat inadvertent overdosage of methotrexate, in which case it must be given immediately. It is also used as an adjunct in chemotherapeutic programmes for the management of several forms of cancer and in combination with fluorouracil in the palliative treatment of advanced colorectal cancer.

**Contraindications:** Hypersensitivity.

**Precautions:** Care should be taken in detecting pernicious anaemia or other megaloblastic anaemias due to vitamin B₁₂ deficiency. Calcium folinate combined with fluorouracil should only be administered under specialist supervision since calcium folinate enhances fluorouracil's toxicity; elderly or debilitated patients are particularly at risk.

**Adverse effects:** Rarely, allergic reactions, and possibility of seizures after parenteral administration.

**CHLORMETHINE**

*Powder for injection: 10 mg (hydrochloride) in vial*

**Uses:** Palliative treatment of Hodgkin disease (Stages III and IV) and some non-Hodgkin lymphomas including lymphosarcoma, chronic myelocytic or chronic lymphocytic leukaemia, polycythaemia vera, mycosis fungoides, and bronchiogenic carcinoma, especially epidermoid, and small-cell carcinomas, malignant effusions of the pericardium, the peritoneum or the pleura.

**Contraindications:** Hypersensitivity. Presence of infectious diseases.

**Precautions:** Should be used with great caution in patients with tumour cell infiltration of bone-marrow. Haematological status should be monitored. Do not administer when leukocyte count is less than 1000/mm³ or the platelet count is less than 50 000/mm³. Patients should be told to report promptly any signs of sore throat, fever, unusual bleeding or bruising.

**Adverse effects:** Nausea, severe vomiting, diarrhoea, and anorexia can occur commonly. Irregular menstruation, precipitation of herpes zoster, myelosuppression resulting in increased susceptibility to infections, thrombocytopenia, and ototoxicity (at high doses) have frequently been reported including hyperuricaemia, thrombosis, thrombophlebitis or extravasation, and alopecia. Allergic reactions, peripheral neuritis, hepatotoxicity, and peptic ulcer occur rarely.

**CISPLATIN**

*Powder for injection: 10 mg, 50 mg in vial*

**Uses:** Treatment of metastatic testicular tumours, metastatic ovarian tumours, advanced bladder carcinoma and other neoplasms.

**Contraindications:** Hypersensitivity; renal or hearing impairment; myelosuppression.

**Precautions:** Administer only under specialist supervision, monitor blood counts, liver function and renal function weekly and perform neurological examination regularly. Hydrate.

**Adverse effects:** Commonly, nausea, vomiting and nephrotoxicity occur for which mandatory hydration should be given before initiating treatment. Myelosuppression, ototoxicity, neurotoxicity and other toxicities may be severe enough to necessitate dosage reduction or withdrawal. Serum electrolyte disturbances include hypomagnesaemia, hypocalcaemia, hyponatraemia, hypokalaemia, hypophosphataemia. Ocular toxicity and anaphylactic reactions, liver enzyme concentration elevations, cardiac abnormalities, anorexia, and alopecia have also been reported.

**CYCLOPHOSPHAMIDE**

*Tablet: 25 mg Powder for injection: 500 mg in vial*

**Uses:** Used alone, concurrently or sequentially with other antineoplastic drugs in the treatment of malignant lymphomas, Hodgkin disease, lymphocytic lymphoma, Burkitt lymphoma, multiple myeloma, leukaemias, mycosis fungoides, neuroblastoma, adenocarcinoma of the ovary, retinoblastoma, and carcinoma of the breast.

**Contraindications:** Hypersensitivity; severe bone-marrow depression.

**Precautions:** Only to be administered under specialist supervision. Monitor the full blood count and if myelosuppression occurs, withdraw until the blood and platelet count return to normal. Caution is needed in patients with leukopenia, thrombocytopenia, tumour cell infiltration of bone-marrow, previous X-ray therapy, previous treatment with other anti-neoplastic drugs, impaired renal or hepatic function. Extreme care required with invasive procedures in patients who develop thrombocytopenia during treatment.
Adverse effects: Potentially serious haemorrhagic cystitis can occur rarely. Adequate hydration is mandatory prior to, and for at least 72 hours after administration. Discontinue if haemorrhagic cystitis occurs. Reversible myelosuppression, nausea, vomiting, and anorexia commonly occur. Alopecia, interstitial pulmonary fibrosis (during prolonged treatment with high doses), metabolic effects include hyperuricaemia, cardiotoxicity (which may be fatal), headache, dizziness, myxoedema, and delayed wound healing frequently occur. Occasionally, diarrhoea, haemorrhagic colitis, stomatitis and, rarely, hepatotoxicity and anaphylactic reactions have been reported.

CYTARABINE
Powder for injection: 100 mg in vial
Uses: Treatment of acute lymphocytic leukaemia, acute or chronic myelocytic leukaemia, prophylaxis and treatment of meningeval leukaemia, erythro-leukaemia, and non-Hodgkin lymphoma.
Contraindications: Hypersensitivity.
Precautions: Take frequent platelet and blood counts, and bone-marrow examination. Should be used with caution in patients with drug-induced bone-marrow depression.
Adverse effects: Dose-related myelosuppression, anaemia, leukopenia, thrombocytopenia, megaloblastosis, reduced reticulocytopenia, increased susceptibility to infections, and anaphylactic-like reactions may occur. Nausea and vomiting which may follow rapid intravenous injection, anorexia, mucositis, stomatitis, hepatotoxicity, thrombophlebitis, and haemorrhagic complications have been frequently reported and, less frequently, abdominal pain, urinary retention, renal dysfunction, neural toxicity, allergic skin reactions, and alopecia.

DACARBAZINE
Powder for injection: 100 mg in vial
Uses: Treatment of metastatic malignant melanoma, and as first-line therapy for Hodgkin disease in combination with other antineoplastic agents.
Contraindications: Hypersensitivity.
Precautions: Hospitalization is not always necessary, but adequate facilities are required for monitoring of full blood count and for bone-marrow examination.

Adverse effects: Withdraw the drug if severe myelosuppression occurs. This may result in thrombocytopenia and leucopenia which may be fatal. Frequently, nausea, vomiting and anorexia have been reported. Hepatotoxicity with hepatic vein thrombosis and hepatocellular necrosis, diarrhoea, influenza-like syndrome with fever, malaise and myalgia, alopecia, facial flushing, facial paraesthesia, erythematous and urticarial rashes, and photosensitivity may rarely occur.

DACTINOMYCIN
Powder for injection: 500 µg in vial
Use: In combination with other antineoplastic agents for the treatment of endometrial carcinoma, trophoblastic tumours, testicular carcinoma, Wilm tumour, Ewing sarcoma, rhabdomyosarcoma.
Contraindications: Hypersensitivity, herpes zoster or chickenpox.
Precautions: Periodic monitoring of hepatic function.
Adverse effects: Amenorrhoea, breakthrough bleeding, irregular menstruation, and weight gain frequently occur. Dose-related oedema, muscle cramps and spasms, virilism, bladder telangiectasia, thrombocytopenia, bleeding gums and hepatic dysfunction have been reported less frequently.

DOXORUBICIN
Powder for injection: 10 mg, 50 mg (hydrochloride) in vial
Uses: Treatment of acute lymphocytic and myelocytic leukaemias, treatment of carcinomas of the breast, bladder, ovary and thyroid, neuroblastoma, Wilm tumour, non-Hodgkin and Hodgkin lymphomas, soft tissue sarcomas, osteosarcoma.
Contraindications: Hypersensitivity. Previous treatment with full cumulative doses of doxorubicin, daunorubicin, or other anthracyclines and anthrancenes, myelosuppression induced by drug or radiation therapy.
Precautions: The probability of cardiomyopathy increases if the cumulative dose exceeds 450 mg/m² body surface area. Use with caution in patients with previous cardiac disease or those who have received previous myocardial radiation therapy. Cardiac monitoring may be necessary and a blood count is required before initiation of
therapy, and weekly thereafter. May cause severe tissue necrosis if extravasation occurs. Reduce dosage in patients with renal or hepatic impairment.

**Adverse effects:** Dose-limiting myelosuppression and cardiomyopathy may occur and, frequently, nausea, severe vomiting, mucositis including stomatitis and oesophagitis, ulceration and necrosis of the colon resulting in bleeding or acute infections which may be fatal (especially in non-lymphocytic leukaemia), complete but reversible alopecia, hyperpigmentation of nail-beds and dermal creases, and sometimes onycholysis. Rarely, secondary acute myeloid leukaemia with or without preleukaemic phase, hypersensitivity reactions which include fever, chills and urticaria, facial flushing on rapid i.v. injection have been reported.

**ETOPOSIDE**
*Capsule:* 100 mg  
*Injection:* 20 mg/ml in 5-ml ampoule

**Uses:** In combination with other antineoplastic agents for treatment of refractory testicular tumours in patients who have received appropriate surgical, chemotherapeutic and radiation therapy. In combination with other agents for treatment of small-cell lung carcinoma.

**Contraindications:** Hypersensitivity.

**Precautions:** Close monitoring for possible hypotensive or anaphylactoid reactions. Resuscitation facilities should be readily available. Full blood counts should be taken before and at weekly intervals during therapy.

**Adverse effects:** Dose-related and dose-limiting myelosuppression, nausea, vomiting, transient hypotension following intravenous administration, anaphylactoid reactions including chills, fever, bronchospasm and dyspnoea may occur. Infrequently, rashes, fever, pruritus, abdominal pain, constipation, dysphagia, and transient corneal blindness have been reported.

**FLUOROURACIL**
*Injection:* 50 mg/ml in 5-ml ampoule

**Uses:** Carcinomas of the colorectum, breast, stomach, pancreas, bladder, cervix, prostate, ovary and endometrium, liver tumours, head and neck tumours.

**Contraindications:** Hypersensitivity, poor nutritional status, severe bone-marrow depression, potentially serious infections.

**Precautions:** Should be used with caution in renal or hepatic impairment.

**Adverse effects:** Commonly, nausea, vomiting, stomatitis, diarrhoea, anorexia, leukopenia, alopecia, dermatitis, and acute cerebellar syndrome which may persist after discontinuation, may occur.

**LEVAMISOLE**
*Tablet:* 50 mg (as hydrochloride)

**Uses:** In combination with fluorouracil for the treatment of colorectal carcinoma after complete resection of primary tumour with little or no evidence of local or distant metastases.

**Contraindications:** Hypersensitivity.

**Precautions:** Haematological monitoring essential because of the risk of agranulocytosis which may be fatal. Patients should be instructed to report any signs of fever, chills or unusual discomfort or weakness.

**Adverse effects:** When used as a single agent, effects are usually mild; however, when combined with fluorouracil, haematological and gastrointestinal effects may frequently occur. Less frequently, blood dyscrasias including agranulocytosis, leukopenia or thrombocytopenia, mild stomatitis are also reported. CNS toxicity (including ataxia, confusion, and paranoia, seizures, tardive dyskinesia), exfoliative dermatitis, periorbital oedema, hallucinations, elevation of serum creatinine and alkaline phosphatase may rarely occur.

**MERCAPTOPURINE**
*Tablet:* 50 mg

**Uses:** Treatment of acute lymphocytic, acute myelocytic and acute myelomonocytic leukaemias.

**Contraindications:** Hypersensitivity.

**Precautions:** Weekly blood count and hepatic function monitoring necessary.

**Adverse effects:** Potentially serious myelosuppression frequently occurs leading to leukenemia, thrombocytopenia and anaemia which can be life-threatening, hepatotoxicity or biliary stasis. Less
frequently, hyperuricaemia, nausea, vomiting and anorexia, gastrointestinal ulceration, and stomatitis are reported.

**METHOTREXATE**

*Tablet: 2.5 mg (as sodium salt)*  
*Powder for injection: 50 mg (as sodium salt) in vial*

**Uses:** Carcinoma of the breast, head, neck, and lung. Trophoblastic tumours, acute lymphocytic leukaemia. Prophylaxis and treatment of meningeal leukaemia, treatment of non-Hodgkin disease including advanced cases of lymphosarcoma, and advanced cases of mycosis fungoides. In combination with other antineoplastic agents, for treatment of non-metastatic osteosarcoma in patients who have undergone primary surgical treatment.

**Contraindications:** Severe renal or hepatic impairment, pregnancy, breast-feeding.

**Precautions:** Complete haematological analysis should be undertaken before treatment is initiated including renal and hepatic function tests, followed by weekly monitoring throughout. Use with extreme caution in cases of peptic ulceration, ulcerative colitis and diarrhoea. Withdraw if stomatitis occurs since this may be the first sign of gastrointestinal toxicity.

**Adverse effects:** Pulmonary toxicity, photosensitivity, hepatic toxicity, haematological toxicity, and gastrointestinal toxicity have been reported.

**Drug interactions:** Concurrent administration of acetylsalicylic acid or NSAID may reduce excretion of methotrexate and increase its toxicity. Patients should be advised not to use over-the-counter preparations without consulting the physician in charge of palliative treatment.

**PROCARBAZINE**  
*Capsule: 50 mg (as hydrochloride)*

**Uses:** As part of MOPP chemotherapy in Hodgkin disease, and non-Hodgkin lymphoma.

**Contraindications:** Hypersensitivity, severe bone-marrow depression.

**Precautions:** The patient should be hospitalized for initiation of treatment. Periodic determination of blood counts is necessary. Alcohol may cause disulfiram-like reaction.

**Adverse effects:** Myelosuppression, nausea and vomiting, anorexia, abdominal pain, stomatitis, and dryness of mouth may commonly occur. Other effects include paraesthesia, neuropathy, depression, psychosis, hallucination, myalgia and arthralgia, lethargy, dermatitis, rash, pruritus and infections.

**VINBLASTINE**  
*Powder for injection: 10 mg (sulfate) in vial*

**Uses:** Alone or in combination with other antineoplastic agents as a palliative during treatment of disseminated Hodgkin (stage III and IV) and non-Hodgkin lymphoma. It may also be used in combination with other agents for treatment of advanced testicular carcinoma, breast carcinoma unresponsive to endocrine surgery or hormonal therapy, and alone or in combination as a palliative agent for Kaposi sarcoma, trophoblastic tumours, Letterer-Siwe disease, or mycosis fungoides.

**Contraindications:** Hypersensitivity, drug-induced granulocytopenia, severe infection.

**Precautions:** Avoid contact with eyes as vinblastine may cause severe irritation or corneal ulceration. Patients should be advised to report signs of fever, sore throat, unusual bleeding or bruising because the risks of myelosuppression may be fatal. Use with caution in debilitated or elderly patients.

**Adverse effects:** Myelosuppression may occur frequently. Infections, nausea, vomiting, hyperuricaemia or uric acid nephropathy, stomatitis, transient thrombocytopenia, extravasation have been reported. Rarely, haemorrhagic colitis, bleeding from previous peptic ulcers, and neurotoxicity may occur.

**VINCRISTINE**  
*Powder for injection: 1 mg, 5 mg (sulfate) in vial*

**Uses:** Acute lymphocytic lymphoma, neuroblastoma, Wilm tumour, Hodgkin and non-Hodgkin lymphomas, rhabdomyosarcoma, Ewing sarcoma.

**Contraindications:** Hypersensitivity.

**Precautions:** Use with caution in patients with pre-existing neuromuscular disorder or those receiving other neurotoxic drugs, avoid contact with eyes, as it may cause severe irritation or corneal ulceration.
**Adverse effects:** Neurotoxicity (as peripheral neuropathy), constipation, abdominal cramps, and alopecia which is reversible on cessation of therapy occur commonly. Less frequently, hyponatraemia as a syndrome of inappropriate ADH secretion, extravasation, allergic reactions such as anaphylaxis, rash and oedema, hypertension, hypotension, stomatitis, intestinal necrosis and perforation have been reported.

**Hormones and antihormones**

Diethylstilboestrol (DES) is a synthetic estrogen. It is used to manipulate the hormonal environment in patients with tumours of hormonally sensitive organs (breast and testes). It has little toxicity in women, but in men it causes gynaecomastia and, more importantly, increases the risk of cardiovascular disease. The use of DES and other estrogens in breast cancer has largely been supplanted by tamoxifen. However, it can be employed to suppress androgen production in patients with prostate cancer, and can play an important palliative and possibly adjuvant role.

The corticosteroids prednisolone, dexamethasone, and hydrocortisone are synthetic hormones given at pharmacological doses, particularly for haematological malignancies. Their precise mechanism of action is not known, but they appear to be cytolytic, at least in lymphoid diseases. Although there is no evidence of therapeutic superiority, prednisolone is a commonly used component of antineoplastic regimens. However, chronic use leads to the toxicity associated with Cushing syndrome. Toxicity of corticosteroids is generally experienced as insomnia, and as hyperglycaemia in diabetics. Prednisolone is an important component of curative regimens for lymphomas and childhood leukaemias, and elsewhere it has a palliative role.

Tamoxifen antagonizes the effects of estrogen despite its estrogenic properties. When given at recommended doses, it has few adverse effects, although it can induce uterine malignancies. Its major role in cancer therapy is use after surgery and for palliative management in patients with breast cancer.

**PREDNISOLONE**

**Tablet:** 5 mg

**Powder for injection:** 20 mg, 25 mg, (as sodium phosphate or sodium succinate) in vial

**Uses:** In combination with antineoplastic agents, for the palliative treatment of acute or chronic lymphocytic leukaemia, Hodgkin and non-Hodgkin lymphoma.

**Dosage:**

**Adults:** 60–100 mg daily or even higher for the first few days, with gradual reduction to 20–40 mg daily.

**Children:** 0.5 mg/kg or 15 mg/m² four times daily for 2–3 weeks, followed by 0.375 mg/kg or 11.25 mg/m² four times daily for 4–6 weeks.

**Contraindications:** Known hypersensitivity to any corticosteroid. Active bacterial, viral or fungal infection. Unless the benefits outweigh the risks, systemic administration of corticosteroids is contraindicated in patients with peptic ulcer, osteoporosis, psychoses or severe psychoneuroses, congestive heart failure, hypertension, diabetes mellitus, epilepsy, glaucoma, ocular herpes simplex, chronic renal failure or uraemia.

**Precautions:** Monitor body weight, blood pressure, fluid and electrolyte balance, and blood glucose concentrations throughout treatment. The response to the pituitary-adrenal axis is reduced and may remain depressed for many months after withdrawal of the drug. If an infection occurs during this period, prednisolone therapy may need to be reinstated temporarily.

Children on corticosteroid therapy should be treated with immunoglobulin if they are exposed to a childhood viral infection to which they have no acquired immunity. They should not receive live-virus vaccines. To reduce the risk of stunted growth, intermittent dosage regimens should be used for children when therapy is prolonged for more than 6 months.

**Adverse effects:** Infections contracted during therapy can be fatal in the absence of effective treatment. Quiescent tuberculosis may be reactivated.

Long-term treatment at doses of approximately 10 mg daily may result in stunting of growth in children — which may be averted by giving corticotrophin and selected alternate-day dosage schedules. Effects include hypercorticalism, moon face, acne, bruising, abdominal striae, truncal obesity, muscle-wasting, hypertension, and amenorrhoea and hirsutism in females, spinal osteoporosis and vertebral collapse (which may be retarded by giving calcium supplements and small doses of vitamin D), aseptic osteonecrosis, particularly of the femo-
ral head, subcapsular cataracts and glaucoma, development or aggravation of peptic ulcers, diabetes mellitus, depression and psychosis, with risk of suicide, raised intracranial pressure and convulsions, particularly in children, increased coagulability of blood, delayed tissue healing, myopathy characterized by weakness of the proximal musculature of arms and legs.

**TAMOXIFEN**  
*Tablet: 10 mg, 20 mg (as citrate)*

**Uses:** As adjuvant treatment of axillary node-negative breast cancer in women or axillary node-positive breast cancer in postmenopausal women following total or segmental mastectomy. Axillary dissection, and breast irradiation, and treatment of metastatic breast cancer in men and women.

**Dosage:**  
- **Node-negative and node-positive breast cancer in women**  
  10 mg twice daily.  
- **Metastatic breast cancer in men and women**  
  10 or 20 mg twice daily.

**Contraindications:** Hypersensitivity.

**Precautions:** Should be used with caution in patients with severe bone-marrow depression. Periodic blood counts, including platelet counts, are necessary, as well as a periodic liver function test in the rare event of lipoprotein abnormalities. Serum triglycerides and lipoproteins should be monitored in patients with preexisting hyperlipoproteinuria. Ophthalmological examination may be necessary to detect ocular toxicity.

**Adverse effects:** Hot flushes, nausea and vomiting frequently occur in women and the dosage should be reduced if severe. Vaginal bleeding, vaginal discharge, menstrual irregularities, exacerbation of bone pain in patients with bone metastases may occur less frequently. Changes in liver enzyme levels and cholestasis, hepatitis and hepatic necrosis, thromboembolic events, thrombocytopenia hypercalcaemia, dysgeusia, oedema, depression, dizziness, hair thinning or partial alopecia, vaginal dryness, uterine fibroids, risk of endometrial cancer, visual disturbances including corneal changes, cataracts and retinopathy have rarely been reported.

**Drugs used in palliative care**

Palliative care for cancer patients includes both pain relief and the symptomatic relief of dyspnoea, restlessness, confusion, anorexia, constipation, pruritus, nausea, vomiting and insomnia.

Pain relief can be achieved by treatment with drugs or anaesthetics and neurosurgical, psychological and behavioural approaches geared to individual patient needs. If carried out correctly, most patients with cancer pain can obtain effective relief. Pain is best treated with a combination of drug and non-drug measures. Analgesics and other drugs constituting the basis of cancer pain management are described in the WHO publication *Cancer Pain Relief (1).*

Anticancer therapy and drugs for cancer pain can be given concurrently. Some types of pain respond well to a combination of non-opioid and opioid treatment. With others, relief is obtained by combining a corticosteroid and an opioid. Neuropathic pains often show little response to non-opioids and opioid analgesics, but may be eased by tricyclic antidepressants and anticonvulsants.

Recognizing when neuropathic pain is resistant to opioids is important for optimal drug treatment. Cancer patients often have many fears and anxieties, and may become depressed. Very anxious or deeply depressed patients may need an appropriate psychotropic drug in addition to an analgesic. If this fact is not appreciated, the pain may remain intractable.

In the majority of patients, cancer pain can be relieved with analgesics. If possible, these should be given orally. Rectal suppositories are useful in patients with dysphagia, uncontrolled vomiting or gastrointestinal obstruction. Continuous subcutaneous infusion offers an alternative.

**Timing:** An analgesic should be given at fixed time intervals and titrated against the degree of pain. In this way, the next dose can be given before the effect of the previous one has fully worn off.

The first and last doses of the day should be linked to the patient’s waking time and bedtime. Ideally, the drug regimen should be written clearly for the patient and the care provider to follow. The patient should be warned in advance about possible adverse effects.
**Using the WHO analgesic ladder concept.** The first step will be to give a non-opioid analgesic such as acetylsalicylic acid, paracetamol or ibuprofen and, if necessary, an adjuvant drug. If this does not relieve the pain, an opioid for mild to moderate pain such as codeine should be added. When this combination fails to relieve pain, an opioid for moderate to severe pain such as morphine should be substituted.

**Individually tailored:** There are no standard doses for opioid drugs. The range for oral morphine is from as little as 5 mg to more than 1000 mg every 4 hours.

**Drugs for neuropathic pain:** Patients with neuropathic pain may derive benefit from opioids with or without a corticosteroid, particularly in the case of nerve compression. Alternatively, neuropathic pain often responds to a tricyclic antidepressant, such as amitriptyline, an anticonvulsant such as carbamazepine or a local anaesthetic such as intravenous lidocaine.

**Adjuvant therapy** may be necessary for any one of three reasons:

- to treat the adverse effects of the analgesics, e.g. antiemetics such as metoclopramide and laxatives.
- to support other pain relief methods, e.g. a corticosteroid such as prednisolone in nerve compression pain.
- to treat concomitant psychological disturbances such as insomnia, anxiety and depression.

Reference:

Recent Publications and Documents

Guidance for industry: active pharmaceutical ingredients

This document focuses on the manufacture of active pharmaceutical ingredients (APIs) and will provide guidance to industry on basic requirements expected when filing for or renewing new drug applications within the United States of America. It may also prove useful for the manufacture of excipients.

For the moment, the document is circulated as a draft for comments and is not meant for implementation. However, it will give a good indication of the requirements desired in the manufacture and control of APIs for drugs and biologicals, including chemical isolation and purification steps used for biological or fermentation processes and sterile APIs. It does not apply to medical gases, bulk packaged drug products in final dosage form, and radiopharmaceuticals.

Good manufacturing practices apply to all steps of the API manufacturing process, including the use of starting materials. Such practices include the validation of processes determined to affect the quality and purity of the active pharmaceutical ingredient.

Draft guidance for industry: manufacturing, processing or holding active pharmaceutical ingredients. Available from: Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville MD 20852, USA or through http://www.fda.gov/cber.

Guidance for industry: human plasma-derived biological products

The Food and Drug Administration has announced the availability of a draft guidance for industry for the establishment of descriptive information for human plasma-derived biologicals or animal plasma or serum-derived products. The guidance is intended to assist applicants in the preparation of the descriptive section of a licence application for such products. This action is intended to reduce unnecessary burdens for industry without diminishing public health protection.

Draft guidance for industry for the submission of chemistry, manufacturing and controls and establishment description information for human plasma-derived biological products or animal plasma or serum-derived products. Available from: Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville MD 20852, USA or through http://www.fda.gov/cber.

WHO Expert Committee on Drug Dependence

The scale of drug dependence has grown dramatically in the past quarter-century. Preventing dependence and reducing the harm associated with the use of psychoactive substances is a challenge for health services and governments the world over. This WHO Expert Committee report categorizes the different types of harm that can result from psychoactive substances, whether illicit or legally available, and describes the steps that can be taken to treat health problems and stop them from occurring. The report looks at the cost and effectiveness of various treatment methods, drawing on evidence from research findings, and gives a detailed outline of the elements needed for an effective national treatment system. It addresses the question of whether dependent persons should be given a controlled supply of drugs and proposes for further review several substances that have potential for abuse. The Expert Committee's recommendations cover drug policies and treatment services, as well as training, information needs and research. The report lays the foundation for realistic but sound strategies in national and international efforts to reduce the health damage caused by the use of psychoactive substances.

Recent Publications and Documents

**WHO Expert Committee on Biological Standardization: Forty-sixth report**

This report represents the recommendations of a WHO expert committee commissioned to coordinate a range of research and other activities required to assure the purity, potency, safety and stability of biological products used in medicine. The report covers the development and adoption of detailed requirements for the manufacturing, licensing and control of vaccines and other biologicals. The committee also coordinates the establishment of international biological reference materials for use in clinical assays, pharmaceutical research and quality control.

The report is divided into three parts. The first provides a brief discussion of general issues that shape the committee’s work. Issues discussed include procedures for establishing and distributing reference materials and the rationale for issuing or revising requirements for specific products. The second part summarizes activities relating to the status of some 36 biological reference preparations categorized as antibiotics, antibodies, antigens and related substances; blood products, cytokines, endocrinological substances and toxins.

The third and most extensive part contains detailed revised requirements for the production and control of yellow fever vaccine and amended general requirements for the sterility of biological substances, modified to reflect new procedures for conducting a sterility test for mycoplasmas. Also included are a list of laboratories approved by WHO for the production of yellow fever vaccine and a summary protocol for the routine batch release of virus vaccines.

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**Use of antimicrobials in food-producing animals**

In October 1997, the World Health Organization convened a meeting to examine the question of whether the use of antimicrobials in livestock production contributes to the escalation of antimicrobial resistance in humans. Timely public health action is needed to control medical problems related to the widespread application of antimicrobials outside the medical sphere. On the agenda were such issues as the development, licensing and use of antimicrobials in livestock production, and clinical microbiology, resistance monitoring and medical infectious disease control.

The meeting reviewed antimicrobial use and the known and potential consequences in food animal production. General recommendations were proposed for action by national control authorities and collaboration within the medical, veterinary and agricultural sectors. It was agreed that WHO should take the lead in coordinating international efforts in resistance monitoring. As a matter of urgency, microbiological laboratories capable of developing networks on resistance monitoring should be strengthened. In this way, countries will be able to ascertain and monitor the prevalence of resistant bacteria in food-producing animal products.

The use of antimicrobials in animals must balance the possible benefits to livestock production against the medical risk and public health consequences deriving from their use. It was emphasized that antimicrobial agents should not be used as a substitute for adequate hygiene in animal husbandry. No antimicrobial should be administered to a food animal unless it has been evaluated and authorized by the national authorities, and prescription and practice standards should be strictly applied.

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*The medical impact of the use of antimicrobials in food animals: available from the Division of Emerging and Other Communicable Diseases, Surveillance and Control. WHO, Geneva. WHO/EMC/ZOO/97.4.*
International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names (Rec. INN): List 40

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. World Health Org., 1955, 60, 3 (Resolution EB15.77); 1969, 173, 10 (Resolution EB43.99)], 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 40


Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS (DCI Rec.): Lista 40

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.
An ongoing review is under way of the long-standing objections to proposed International Nonproprietary Names (INN). As a result, objections have been withdrawn to the following names which are now included in this list of recommended INNs:

alfacalcidol, almecillin, alverine, amiflamine, anazolene sodium, calcium pantothenate, chloralose, dimepranol, elanzepine, elfazepam, esmolol, fenisorex, fibrinolysin (human), flavamine, glucosamine, iometin (131 l), iometin (125 l), leucocianidol, levocarnitine, lombazole, loprodiol, metformin, mianserin, midaflur, neocinchophen, ribavirin, ropizine, soterenol, sulmazole, thiomersal

Les objections formulées de longue date contre des Dénominations communes internationales (DCI) proposées sont examinées. Des objections ont été retirées à la suite de cet examen et les noms suivants sont donc inclus dans cette liste des DCI recommandées:

alfacalcidol, almécilline, alvérine, amiflamine, anazolene sodique, pantoténate de calcium, chloralose, dimépranol, élanzépine, elfazépam, esmolol, fénisorex, fibrinolysine (humaine), flavamine, glucosamine, iométine (131 l), iométine (125 l), leucocianidol, lévocarnitine, lombazole, loprodiol, metformine, miansérine, midaflur, néocinchophène, ribavirine, ropizine, sotérénil, sulmazole, thiomersal

Se ha emprendido un examen de las objeciones que se vienen formulando desde hace tiempo a las denominaciones comunes internacionales (DCI) propuestas. Como resultado, se han retirado las objeciones a las denominaciones siguientes, que ahora están incluidas en la presente lista de DCI recomendadas:

alfacalcidol, almecilina, alverina, amiflamina, anazolene sódico, pantotenato de calcio, cloralosa, dimepranol, elanzipina, elfazepam, esmolol, fenisorex, fibrinolisina (humana), flavamine, glucosamina, iometina (131 l), iometina (125 l), leucocianidol, levocarnitina, lombazol, loprodiol, metformina, mianserina, midaflur, neocincofeno, ribavirina, ropizina, soterenol, sulmazol, thiomersal
abarelixum
abarelix


abarélix

[N-acétyl-3-(naphtalén-2-yi)-D-alanyl]-(4-chloro-o-phénylalanil)-[3-(pyridín-3-yl)-D-alanyl]-L-seryl-[N-méthyL-L-tyrosyl]-L-asparaginyl-L-leucyl-[N²-(1-méthyléthyL)-L-lysyl]-L-proply-D-alaninamide

abarelíx


acidum minodronicum
minodronic acid

(1-hydroxy-2-imidazo[1,2-a]pyridín-3-yléthylidène)diphosphonico acid

acide minodronique
ácido minodrónico

ácido minodrónico

C₂₀H₁₅N₂O₇P₂
**alfacalcidolum**

(5Z,7E)-9,10-secocholesta-5,7,10(19)-triene-1α,3β-diol

**alfacalcidol**

(5Z,7E) (1R,3R)-9,10-secocholesta-5,7,10(19)-triene-1,3-diol

**alfacalcidol**

(5Z,7E)-9,10-secocholesta-5,7,10(19)-triene-1α,3β-diol

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**almeccillinum**

[(allylthio)methyl]penicillin

**almeccilin**

aci de (2S,5R,6R)-3,3-diméthyl-7-oxo-6-[2-[(prop-2-ényl)sulfanyl]acétyl] amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylique

**almediline**

[(allylthio)methyl]penicillina

C₁₃H₁₆N₂O₄S₂

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**alverinum**

N-ethyl-3,3'-diphenyldipropylamine

**alverine**

N-éthyl-3-phényl-N-(3-phénylpropyl)propan-1-amine

**alverina**

N-ethyl-3,3'-difenildipropilamina

C₂₀H₂₇N
amiflaminum
amiflamine
amiflamine
amiflamina

(+)-4-(dimethylamino)-α,2-dimethylphenethylamine

\( \text{C}_{12}\text{H}_{20}\text{N}_{2} \)

anazolenum natricum
anazolene sodium
anazolène sodique
anazoleno sódico

4-[(4-amino-5-sulfo-1-naphthyl)azo]-5-hydroxy-2,7-naphthalenedisulfonic acid, trisodium salt

4-hydroxy-5-[4-(phénylamino)-5-sulfonatonaphthalén-1-yl]diazenyl]naphthalène-2,7-disulfonate de trisodium

sal trisódica del ácido 4-[(4-anilino-5-sulfo-1-naftil)azo]-5-hidroxi-2,7-naftalenodisulfônico

\( \text{C}_{26}\text{H}_{16}\text{N}_{3}\text{Na}_{3}\text{O}_{10}\text{S}_{3} \)

atreleutonum
atreleuton
atréleuton
atreleutón

1-[(R)-3-[5-(p-fluorobenzyl)-2-thienyl]-1-méthyl-2-propynyl]-1-hydroxyurea

1-[(1R)-3-[5-(4-fluorobenzyl thiophén-2-yl]-1-méthylprop-2-ynyl]-1-hydroxyurea

1-[(R)-3-[5-(p-fluorobenzil)-2-tiênil]-1-méthil-2-propynil]-1-hidroxiurea
RECOMMENDED INN: List 40


C_{14}H_{16}F_{15}N_{2}O_{2}S

aviptadil

\[ \text{isoleucyn-L-} \text{leucyn-L-asparagine} \]

C_{22}H_{23}N_{3}O_{2}

belaperidone

\((+)-3\{-2\{1\{5,5,5\}-6\text{-}p\text{-fluorophenyl}\}3\text{-azabiciclo[3.2.0]hept-3-yl}\text{ethyl}\}-2,4(1H,3H)\text{-quinazoline-2,4-dione} \)

\((+)-3\{-2\{1\{5,5,5\}-6\text{-}4\text{-fluorophenyl}\}3\text{-azabiciclo[3.2.0]hept-3-yl}\text{ethyl}\}=\text{quinazoline-2,4(1H,3H)-dione} \)

\((+)-3\{-2\{1\{5,5,5\}-6\text{-}p\text{-fluorofenil}\}3\text{-azabiciclo[3.2.0]hept-3-yl}\text{ethyl}\}2,4(1H,3H)\text{-quinazolinadiona} \)

C_{22}H_{23}FNO_{2}S
bepotastinum
bepotastine
(+)-4-[[S]-p-chloro-α,2-pyridyloxy]piperidinebutyric acid
bepotastine
acid (+)-4-[5-(4-chlorophenyl)(pyridin-2-yl)methoxy]piperidin-1-ylbutanoïque
bepotastina
ácido (+)-4-[[S]-p-cloro-α-2-piridilbenzo[a]oxi]-1-piperidinabutilico

\[
\text{C}_{21}\text{H}_{25}\text{ClN}_{2}\text{O}_{3}
\]

bibapcitidum
bibapcitide
13,13'-[[oxybis[metilenes(2,5-dioxo-1,3-pyrrolidinadiyl)]]bis[\{\{N-(mercaptoacetyl)-\-
\text{o-tyrosyl-S-}{(3-aminopropyl)}\}-\text{l-cysteinylglycyl-L-}\text{o-aspartyl-}
\text{l-cysteinylylglycyl-S-(acetamidomethyl)}\}-\text{cysteinylylglycyl-S-(acetamidomethyl)}\}-
\text{l-cysteinylglycyl-L-cysteinamide cyclic (1-5), (1'-5')-bis(sulfide)}

bibapotide
{1-5), (1'-5')-bis[sulfure cyclique du 13,13'-[oxybis[metilenes(2,5-
dioxopyrroldine-1,3-diy)]bis[\{\{N-(sulfanylacétyl)-\text{o-tyrosyl)}\]-\text{l-cysteinylglycyl-L-}\text{o-aspartyl-L-cystéinyl-glycyl-glycyl-S-}{[\text{acytynamino)méthyl]}-L-cystéinylglycyl-S-}{[\text{acytynamino)méthyl]}-L-cystéinylglycyl-L-cystéinamide]

bibapotide
{1-5), (1'-5')-bis(sulfuro cíclico de 13,13'-[oxibis[metilenes(2,5-dioxo-1,3-
parroldinadiyl)]]bis[\{\{N-(mercaptoacetyl)-\text{o-férol-S-}{(3-aminopropil)}\}-\text{l-cisteinilglicil-}
\text{l-o-aspartil}-\text{l-cisteinilglicil-glicil-glicil-S-}{(acetamidomethyl)}\}-\text{l-cisteiniglicil-L-}
\text{l-cisteinamidica, cíclica}

\[
\text{C}_{152}\text{H}_{162}\text{N}_{36}\text{O}_{43}\text{S}_{10}
\]

biricodarum
biricodar
4-(3-pyrind)-1-\{3-[3-pyrild]propyloxy]propyl\}butyl (S)-1-\{3,4,5-
triméthoxyphényl]glyoxyloxy]picoate

biricodar
[2S]-1-\{2-oxo-2-(3,4,5-triméthoxyphényl]acétyl\}péridine-2-carboxylate de
4-(pyridin-3-y)l-1-\{3-\text{pyridin-3-yl\}propyloxyl\}butyl

biricodar
(S)-1 \{3,4,5-triméthoxyfenil\}glicoliloji\}picoxolato de 4-(3-piridil)-1-\{3-3-
piridil\}propyloxy]butilo
calcium pantothenate
calcium bis[(R)-N-(2,4-dihydroxy-3,3-dimethylbutyryl)-β-alaninate]
cia[2,4-dihydroxy-3,3-dimethylbutyryl]alaninate de calcium
CaH_{18}CaN_{2}O_{10}

chloralose
α-chloralose or (R)-1,2-O-(2,2,2-trichloroethylidene)-α-D-glucopyranose
α-chloralose ou 1,2-O-[2,2,2-trichloroéthylidène]-α-D-glucopyranose
α-cloralose or (R)-1,2-O-(2,2,2-trichloroéthylidène)-α-D-glucopyranose
CaH_{11}Cl_{2}O_{3}

declopramidum
declopramide
4-amino-3-chloro-N-[2-(diethylamino)ethyl]benzamide
4-amino-3-chloro-N-[2-(diéthylamino)éthyl]benzamide
4-amino-3-cloro-N-[2-(dietilamino)etil]benzamida
**Denileukin diftitox**


**Denileukine diftitox**

N-L-méthionyl[387-L-histidine-388-L-alanine]-[1-388]-toxine (souche C7 de *Corynebacterium diphtheriae*)-(388-2')-(2-133)-interleukine 2 (clone pTIL2-21a humain)

**Denileukina diftitox**

N-L-metionil-387-L-histidina-388-L-alanina-1-388-toxina (cepa C7 de *Corynebacterium diphtheriae*) (388-2')-(2-133)-interleukin 2 (clon humano pTIL2-21a)

**MCADDUVDS**

**SGTQGMYDD**

**VVKTVYDGTL**

**TEEPIKQGD**

**SVELEINFET**

**SCINLDWDVI**

**EZEKARQYLEE**

**ANAVNVAQVI**

**AVHMTHELV**

**FYESIINPQ**

**QUEHLLLQLQ**

**LKLIQCLIEE**

**VSLKQSETT**

175
Dimepranolum
Dimepranol
Dimépranol
Dimepranol
\((\pm)-1\text{-}(\text{dimethylamino})\text{-}2\text{-propanol}\)
\(C_5H_{13}NO\)

Dutasteridum
Dutasteride
Dutastéride
Dutasterida
\(\alpha,\alpha,\alpha',\alpha',\alpha'-\text{hexafluoro}\text{-}3\text{-oxo}\text{-}4\text{-aza}\text{-}5\text{e}-\text{androst-1-ene-17β-carboxy-2',5'-xylicide}\)
\(\alpha,\alpha,\alpha',\alpha',\alpha'-\text{hexafluoro}\text{-}3\text{-oxo}\text{-}4\text{-aza}\text{-}5\text{e}-\text{androst-1-ene-17β-carboxi-2',5'-xilida}\)
\(C_{27}H_{30}F_6N_2O_2\)

Ecenofloxacinum
Ecenofloxacin
écénofloxacine
Ecenofloxacino
\((\pm)-7\text{-}[(1R,5S,6S)-6\text{-amino}\text{-}1\text{-methyl}\text{-}3\text{azabicyclo[3.2.0]hept-3-yl}]\text{-}1\text{-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid}\)
\(\alpha\text{-}7\text{-}[(1R,5S,6S)-6\text{-amino}\text{-}1\text{-methyl}\text{-}3\text{azabicyclo[3.2.0]hept-3-yl}]\text{-}1\text{-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylique}\)
\(\alpha\text{-}7\text{-}[(1R,5S,6S)-6\text{-amino}\text{-}1\text{-methyl}\text{-}3\text{azabicyclo[3.2.0]hept-3-yl}]\text{-}1\text{-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naltrixidina-3-carboxílico}\)
\(C_{19}H_{21}FN_4O_3\)
efavirenzum  
**efavirenz**  
(S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one

efavirenz  
(4S)-6-chloro-4-(cyclopropiethynyl)-4-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazin-2-one

efavirenzo  
(S)-6-cloro-4-(ciclopropiétnil)-1,4-dihidro-4-(trifluorometi)-2H-3,1-benzoxazin-2-on

\[
\text{C}_{14}\text{H}_{9}\text{ClF}_3\text{NO}_2
\]

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elanzepinium  
elanzepine  
3-chloro-11-[3-(dimethylamine)propylidene]-5,6-dihyromorphanthridine

elanzapine  
3-(3-chloro-5,6-dihydro-11H-dibenzo[\(\text{e}\),\(\text{f}\)]azepin-11-yli)idene)-N,N-dimethylpropan-1-amine

elanzepina  
3-cloro-11-[3-(dimetilamino)propilideno]-5,6-dihidromorfantindina

\[
\text{C}_{19}\text{H}_{21}\text{ClN}_2
\]

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elfazepamum  
elfazepam  
7-chloro-1-[2-(ethylsulfonyl)ethyl]-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one

elfazépam  
7-chloro-1-[2-(étilsulfoniI)étíl]-5-(2-fluorophény)-1,3-dihidro-2H-1,4-benzodiazépín-2-one

elfazepam  
7-cloro-1-[2-(etilsulfoniI)etíl]-5-(o-fluorofenil)-1,3-dihidro-2H-1,4-benzodiazépín-2-one
**Embusartanum**

**Embusarten**  
**methyl 6-butyl-1-[2-fluoro-4-(o-1H-tetrazol-5-ylphenyl) benzyl]-1,2-dihydro-2-oxoisonicotinate**

**Embusarten**  
**6-butyl-1-[3-fluoro-2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-oxo-1,2-dihydropyridine-4-carboxylate de méthyle**

**Embusartán**  
**6-butyl-1-[2-fluoro-4-(o-1H/tetrazol-5-ylfenil)bencil]-1,2-dihidro-2-oxisonicollina de metilo**

C_{25}H_{32}FN_{2}O_{5}

**Ensaculinum**

**Ensaculin**  
**7-methoxy-6-[3-[4-(o-methoxyphenyl)-1-piperazinyl]propoxy]-3,4-dimethylcoumarin**

**Ensaculine**  
**7-méthoxy-6-[3-[4-(2-méthoxyphényl)pipérazin-1-yl]propoxy]-3,4-diméthyl-2H-chromén-2-one**

**Ensaculina**  
**7-metoxy-6-[3-[4-(o-metoxifenil)-1-piperazini]propoxi]-3,4-dimeticumarina**

C_{26}H_{32}N_{2}O_{5}
eptifibatidum

N<sup>6</sup>-amidino-N<sup>2</sup>-(3-mercaptoacetyl)-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide, cyclic (1-6)-disulfide

(1-6)-dissulfure cyclique de [N<sup>6</sup>-carbamimidoyl-N<sup>2</sup>-(3-sulfanylpropanoyl)-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cystéinamide

C<sub>35</sub>H<sub>49</sub>N<sub>11</sub>O<sub>9</sub>S<sub>2</sub>

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esmololum

(±)-methyl p-[2-hydroxy-(3-isopropylamino)propoxy]hydrocinnamate

3-[4-[(2RS)-2-hydroxy-3-[(1-méthyléthyl)amino]propoxy]phényl]propanoate de méthyle

(±)-p-[2-hidroxi-(3-isapropilamino)propoxi]hidrocinamato de metilo

C<sub>16</sub>H<sub>25</sub>NO<sub>4</sub>

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fandofloxacinum

6-fluoro-1-(5-fluoro-2-pyridyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid

acide 6-fluoro-1-(5-fluoropyridin-2-yl)-7-(4-méthylpipérazin-1-yl)-4-oxo-1,4-dihydroquinoléine-3-carboxylique

acido 6-fluoro-1-(5-fluor-2-piridil)-1,4-dihidro-7-(4-metil-1-piperazinil)-4-oxo-3-quinolina-carboxilico
fasoracetamum
fasoracetam (+)-1-[(R)-5-oxo-2-pyrrolidinyl]carbonyl]pipendine
fasoracétam (+)-1-[(2R)-5-oxopyrrolidin-2-yl]carbonyl]pípéndine
fasoracetam (+)-1-[(R)-5-oxo-2-pirrolidinil]carbonil]piperidina
C_{10}H_{15}N_{2}O_{2}

fenisorexum
fenisorex cis-7-fluoro-1-phenyl-3-isochromanmethylamine
fénisorex [(1RS,3RS)-7-fluoro-1-phényl-3,4-dihydro-1H-2-benzopyran-3-yl]méthanamine
fenisorex cis-1-fenil-7-fluoro-3-isocromanometilarnina
C_{16}H_{15}FNO

fibrinolysinum (humanum)
fibrinolysin (human) an enzyme obtained from human plasma by conversion of profibrinolysin with streptokinase to fibrinolysin
fibrinolysina (humaine) enzyme obtenue à partir de plasma humain par transformation de la profibrinolysine en fibrinolysine à l’aide de streptokinase
fibrinolisina (humana) enzima obtenida a partir del plasma humano por transformación, con estreptoquinasa, de protofibrinolisina en fibrinolisisa
**Fidarestatum**

**Fidarestat**

\[ (+)-(2S,4S)-6\text{-fluoro-2',5'-dioxospiro[chroman-4,4'-imidazolidine]-2-carboxamide} \]

\[ (+)-(2S,4S)-6\text{-fluoro-2',5'-dioxo-2,3-dihydropyrrolo[4,4'-cromène-4,4'-imidazolidine]-2-carboxamide} \]

\[ (+)-(2S,4S)-6\text{-fluoro-2',5'-dioxospiro[4H-cromen-4,4'-imidazolidine]-2-carboxamida} \]

**Flavaminum**

**Flavamine**

\[ 6\text{[d(e)ethyl/amino)méthyl]-3-méthylflavone} \]

**Flavamina**

\[ 6\text{-[d(e)ethyl/amino)méthyl]-3-méthyl-2-phényl-4H-chromén-4-one} \]

**Frovatriptanum**

**Frovatriptan**

\[ (R)-5,6,7,8\text{-téttractionydro-6-(méthyl/amino)crazolé-3-carboxamide} \]

\[ (6R)-6\text{(méthyl/amino)-6,7,8,9-tétreactiondro-5H-crazolé-3-carboxamide} \]

\[ (R)-5,6,7,8\text{-tetractiondro-6-(méthyl/amino)crazolé-3-carboxamide} \]

\[ C_{14}H_{17}N_3O \]
fulvestrantum
fulvestrant
7α-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17β-diol

fulvestrant
7α-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17β-diol

fulvestrant
7α-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17β-diol

C_{32}H_{47}F_{5}O_{3}S

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glucosaminum

glucosamine
2-amino-2-deoxy-β-D-glucopyranose

2-amino-2-désoxy-β-D-glucopyranose

2-amino-2-deoxi-β-D-glucopiranosa

C_{6}H_{13}NO_{5}

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ibutamorenum

ibutamoren
2-amino-N\{(\((\{\phi\})\)2-(benzyl)oxy)-1-[(1-(methylsulfonyl)spiro[indoline-3,4'-piperidin]-1'-yl]carbonyl[ethyl]-2-methylpropionamide

2-amino-N\{(1\{\{\{\phi\}\})\}1-(benzyl)oxy)methyl\}2-1-(methylsulfonyl)-1,2-dihydraspiron[\{indole-3,4'-piperidin]-1'-yl\}2-oxoethyl\}2-methylpropionamide

2-amino-N\{(\((\{\phi\})\)2-(candioxi)-1-[(1-(methylsulfonyl)spiron[\{indoline-3,4'-piperidin]-1'-yl\}carbonyl][ethyl]2-methylpropionamida

C_{27}H_{36}N_{4}O_{5}S

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182
iometinum ([¹²⁵I])
iometin ([¹²⁵I])
iometina ([¹²⁵I])

4-[[3-(dimethylamino)propyl]-amino]-7-[¹²⁵I]iodoquinoline
N-(7-[¹²⁵I]iodoquinoléin-4-yl)-N,N-diméthylpropane-1,3-diamine
4-[[3-(dimetilamino)propil]-amino]-7-[¹²⁵I]iodoquinolina
C₁₄H₁₈IN₃

leucocianidol
leucocianidol
leucocianidol
3,3',4,4',5,7-flavanhexol
3,3',4,4',5,7-flavanhexol
C₁₈H₁₄O₇
levocarnitium
levocarnitine
levocarnitina

(3R)-3-hydroxy-4-(trimethylammonium)butanoate
hidróxido de (L-3-carboxi-2-hidroxipropil)trimetilammonio, sal interna
C7H15NO3

levocetirizinum
levocetirizine
lévocétirizine
levocetirizina

[2-[[4-[[R]-p-chloro-α-phenylbenzyl]-1-piperazinyl]ethoxy]acetic acid
acide 2-[4-[4-(4-chlorophenyl)phénylméthyl]pipérazin-1-yl]éthoxy]acétique
ácido [2-[4-[(R)-p-cloro-α-fenilbencil]-1-piperazinil]etoxi]acético
C21H25ClIN2O3

levosalbutamolum
levosalbutamol
lévosalbutamol
levosalbutamol

(R)-α-[(tert-butylamino)methyl]-4-hydroxy-m-xylene-a,a'-diol
(1R)-2-[(1,1-diméthyléthyl)amino]-1-[4-hydroxy-3-(hydroxyméthyl)phényl]éthanol
(R)-α-[(terc-butilamino)métil]-4-hidroxi-m-xileno-a,a'-diol
C13H21NO3

lombazolum
lornbazole
lornbazole
lombazol

(±)-1-((α-4-biphenylyl-o-chlorobenzyl)imidazole
1-[(RS)-(biphényl-4-yl)(2-chlorophényl)méthyl]-1H-imidazole
(±)-1-(α-4-bifenil-o-clorobencil)imidazol
loprodiol
loprodiol
loprodiol
2,2-bis(chloromethyl)-1,3-propanediol
C₅H₁₀Cl₂O₂

lotrafibanum
lotrafiban
lotrafiban
(S)-2,3,4,5-tetrahydro-4-methyl-3-oxo-7-[(4-[(4-piperidyl)piperidino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid
C₂₃H₃₂N₄O₄

meluadrinum
meluadrine
meluadrine
(-)-(R)-α-[(tert-butylamino)methyl]-2-chloro-4-hydroxybenzyl alcohol
alcohol (-)-(R)-α-[(tert-butylamino)methyl]-2-chloro-4-hydroxybenzyl alcohol
mespiperonum\(^{(11}C)\)
mespiperone\(^{(11}C)\)

\[ 8\text{-[3-[p-fluorobenzyloxy]propyl]-3-[11}C]\text{methyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one} \]

mespipérone\(^{(11}C)\)

\[ 8\text{-[4-(4-fluorophenyl)-4-oxobutyl]-3-[11}C]\text{methyl-1-phenyl-1,3,8-triazaspiro[4.5]décan-4-one} \]

mespiperona\(^{(11}C)\)

\[ 8\text{-[3-[p-fluorobenzyloxy]propyl]-3-[11}C]\text{methyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-on} \]
\[ C_{23}\text{H}_{28}\text{F}_{3}\text{N}_{2}\text{O}_{2} \]

metforminum
metformin

\[ 1,1\text{-dimethylbiguanide} \]

metformine

\[ 1,1\text{-diméthylbiguanide} \]

metformina

\[ 1,1\text{-dimetilbiguanida} \]
\[ C_{4}H_{11}N_{5} \]

mianserinum
mianserin

\[ 1,2,3,4,10,14b\text{-hexahydro-2-methylinden[c,f]pyrazino[1,2-a]azepine} \]

miansérine

\[ (14b\text{RS})\text{-2-méthyl-1,2,3,4,10,14b-hexahydroinden[c,f]pyrazino[1,2-a]azépine} \]

mianserina

\[ 1,2,3,4,10,14b\text{-hexahydro-2-metildibenzo[c,f]pyrazino[1,2-a]azepina} \]
midalflurum
diadflur

4-amino-2,2,5,5-tetakis(trifluoromethyl)-3-imidazoline

C₁₈H₂₀N₂

-enantiomer
et enantiomère

y enantiómero

mitiglinidum

(-)-(2S,3a,7a-cis)-α-benzylhexahydro-γ-oxo-2-isindolinebutyric acid

C₁₉H₂₅NO₃

moxifloxacinum

1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrido[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid

ácido 1-ciclopropil-6-fluoro-1,4-dihidro-8-metoxi-7-[(4aS,7aS)-octahidro-6H-pirrolo[3,4-b]piridin-6-yl]-4-oxo-3-quinolinocárbónico
moxilubant

4-[[5-(p-amidinophenoxy)pentyl]oxy]-N,N-dilsopropyl-3-methoxybenzamide

C₂₁H₂₄FN₃O₄

neocinchophenum

ethyl 6-methyl-2-phenylquinoline-4-carboxylate

C₁₉H₁₇NO₂

nepaduantum

cyclo[N-(2-acetamido-2-deoxy-β-D-glucopyranosyl]-L-asparaginyl-L-asparyl-
L-tryptophyl-L-phenylalanyl-L-2,3-diaminopropionyl]-L-leucyl], cyclic (2-5)-peptide

C₂₆H₃₇N₃O₄

nepaduant

(2-5)-peptide cyclique du cyclo[N-(2-acétylamino)-2-désoxy-
β-D-glucopyranosyl]-l-asparaginyl]-l-aspartyl-L-tryptophyl-L-phenylalanyl]-L-2,3-diaminopropionyl]-L-leucyl]

nepaduant

(2-5)-peptido cíclico de ciclo[N-(2-acetamido-2-desoxi-β-n-glucopiranosil)]-
L-asparaginil-L-α-aspartil-L-triptofil-L-phenilalanil-L-2,3-diaminopropionil]-L-leucil]
C_{15}H_{14}N_{2}O_{2}

nepalenacum
nepalenac 2-(2-amino-3-benzoylphenyl)acetamide
naphénéac 2-(2-amino-3-benzoylphényl)acétamide
nepalenaco 2-(2-amino-3-benzofenil)acetamida

nepicastaum
nepicasta 5-(aminomethyl)-1-[(S)-5,7-difluoro-1,2,3,4-tetrahydro-2-naphthyl]-4-imidazoline-2-thione
nepicasta 5-(aminométhyl)-1-[(2S)-5,7-difluoro-1,2,3,4-tétrahydronaphtalén-2-yl]-1,3-dihydro-2H-imidazole-2-thione
nepicasta 5-(aminometil)-1-[(S)-5,7-difluoro-1,2,3,4-tetrahidro-2-naftil]-4-imidazolina-2-thiona

C_{14}H_{15}F_{2}N_{3}S
nitisinonum
nitisinone 2-(α,α,α-trifluoro-2-nitro-p-toluoyl)-1,3-cyclohexanedione
nitisinone 2-[2-nitro-4-(trifluoromethyl)benzoyl]cyclohexane-1,3-dione
nitisinona 2-(α,α,α-trifluoro-2-nitro-p-toluoyl)-1,3-cyclohexanediona

\[
\text{C}_{14}\text{H}_{10}\text{F}_{3}\text{NO}_{5}
\]

nolatrexedum
nolatrexed 2-amino-6-methyl-5-(4-pyridylthio)-4(3H)-quinazolinone
nolatrexed 2-amino-6-méthyl-5-[pyridin-4-yl]sulfanyl]quinazolin-4(1H)-one
nolatrexed 2-amino-6-méthyl-5-(4-piridiltio)-4(3H)-quinazolinona

\[
\text{C}_{14}\text{H}_{12}\text{N}_{4}\text{OS}
\]

omapatrilatum
omapatrilat (4S,7S,10aS)-octahydro-4-[(S)-α-mercaptohydrocinnamamido]-5-oxo-7H-
pyrido[2,1-b][1,3]thiazepine-7-carboxylic acid
omapatrilate acide (4S,7S,10aS)-5-oxo-4-[(2S)-3-phényl-2-sulfanylpropanoyl]amino]-octahydro-7H-pyrido[2,1-b][1,3]thiazépine-7-carboxylique
omapatrilat álcido (4S,7S,10aS)-octahidro-4-[(S)-α-mercaptoprocinamamido]-5-oxo-7H-
pirido[2,1-b][1,3]tiazepina-7-carboxílico

\[
\text{C}_{19}\text{H}_{24}\text{N}_{2}\text{O}_{4}\text{S}_{2}
\]
**pamiteplasum**

pamiteplase

275-L-glutamic acid-(1-91)-(174-527)-plasminogen activator (human tissue-type protein moiety)

**pamiteplase**

[275-acide L-glutamique]-(1-91)-(174-527)-activateur du plasminogène (de type tissulaire humain)

**pamiteplasa**

275-ácido-L-glutámico -(1-91)-(174-527)-activador del plasminógeno (tipo tisular humano fracción proteica)

C_{2175}H_{3309}N_{627}O_{658}S_{34}

* glycosylation site

**paricalcitolum**

paricalcitol

(7E,22E)-19-nor-9,10-secoergosta-5,7,22-triene-1α,3β,25-triol

paricalcitol

(7E,22E)-(1R,3R)-19-nor-9,10-secoergosta-5,7,22-triene-1,3,25-triol

paricalcitol

(7E,22E)-19-nor-9,10-secoergosta-5,7,22-trieno-1α,3β,25-triol
**Pemetrexedum**

*N-*[^2]-[2-{2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl}ethyl]benzoyl-L-glutamic acid

**Pémetrexed**

Acide (2S)-[^2]-[4-[2-{2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl}ethyl]benzoyl]amino]pentanedioïque

**Pemetrexed**

Ácido N[^2]-[2-{2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl}ethyl]benzoyl]-L-glutámico

C₂₀H₂₁N₂O₆

**Perflonapentum**

Dodecafluoropentane

**Perflonapent**

Dodecafluoropentane

**Perflonapent**

Dodecafluoropentano

C₅F₁₂
perflisopentum
acronym: perflisopent
common name: nonafluor-2-(trifluoromethyl)butane
chemical formula: C_9F_22

perflisopent
acronym: perflisopent
common name: nonafluoro-2-(trifluoromethyl)butane
chemical formula: C_9F_22

perflisopent
acronym: perflisopent
common name: nonafluoro-2-(trifluoromethyl)butane
chemical formula: C_9F_22

perflisopent
acronym: perflisopent
common name: nonafluoro-2-(trifluoromethyl)butane
chemical formula: C_9F_22

pexigananum
acronym: pexiganan
common name: 4-hydroxy-1,1-dimethylpiperidinium hydroxide, octadecyl hydrogen phosphate, inner salt
chemical formula: C_{25}H_{52}NO_4P

pexiganan
acronym: pexiganan
common name: 4-hydroxy-1,1-dimethyl-4-
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pibutidinum
pibutidine
pibutidine
3-amino-4-[[[(2)-4-[[4-(piperidinomethyl)-2-pyridyl]oxy]-2-butenyl]amino]-3-cyclobutene-1,2-dione

pregabalinum
pregabalin
prégabaline
pregabalina
(S)-3-(aminomethyl)-5-methylhexanoic acid

prucalopridum
prucalopríde
prucalopride
4-amino-5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)piperidin-4-yl]-7-benzofurancarboxamide
**rapacuronium bromide**

1-allyl-1-(3α,17β-dihydroxy-2β-piperidino-6α-androstan-16β-yl)piperidinium bromide, 3-acetate 17-propionate

**bromure de rapacuronium**

bromure de 1-[3α-(acétyloxy)-2β-(piperidin-1-yi)-17β-(propanoyloxy)-5α-androstan-16β-yi]-1-{prop-2-ényl)piperidinium

**bromuro de rapacuronio**

bromuro de 1-alil-1-(3α,17β-dihidroxi-2β-piperidino-5α-androstan-16β-il)piperidinio, 3-acetato 17-proponato

\[C_{37}H_{61}BrN_2O_4\]

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**ribavirin**

1-β-α-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide

**ribavirine**

1-β-α-ribofurannosyl-1H-1,2,4-triazole-3-carboxamide

**ribavirina**

1-β-α-ribofuranosil-1H-1,2,4-triazolo-3-carboxamida

\[C_8H_{12}N_4O_5\]
rifalazilum
rifalazil


rifalazilo


rifalazil


C_{51}H_{64}N_{4}O_{13}

robalzotanum
robalzotan

\((R)-3-(dicyclobutylamino)-8-fluoro-5-chromancarboxamide\)

robalzotan

\((3R)-3-(dicyclobutylamino)-8-fluoro-3,4-dihydro-2H-chromène-5-carboxamide\)

robalzotán

\((R)-3-(dicyclobutilamino)-8-fluoro-5-cromancarboxamida\)

C_{18}H_{23}FN_{2}O_{2}
ropizinum
ropizine
ropizina
1-(diphenylmethyl)-4-[[6-methyl-2-pyridinyl]methylene]amino]piperazine
4-(diphenylmethyl)-N-[6-methylpyridin-2-yl(methyl)ene]piperazin-1-amine
1-(difenilmetil)-4-[(6-metil-2-piridil)metileno]amino]piperazina
C₂₄H₂₆N₄

rosiglitazonum
rosiglitazone
rosiglitazone
(±)-5-[[2-(methyl-2-pyridylamino)ethoxy]benzyl]-2,4-thiazolidinedione
(5RS)-5-[[4-[[2-(méthyl(pyridin-2-yl)amino)éthoxy]benzy]thiazolidine-2,4-dione
(±)-5-[[2-(metil-2-piridilamino)etoxi]bencil]-2,4-tiazolidinadionna
C₁₈H₁₉N₃O₃S

seocalcitolum
seocalcitol
seocalcitol
(5Z,7E,22E,24E)-24a,26a,27a-trihomo-9,10-secocholesta-5,7,10(19),22,24-pentaene-1α,3β,25-triol
(5Z,7E,22E,24E;1S,3R)-24a,26a,27a-trihomo-9,10-secocholesta-5,7,10(19),22,24-pentaene-1,3,25-triol
(5Z,7E,22E,24E)-24a,26a,27a-trihomo-9,10-secocholesta-5,7,10(19),22,24-pentaeno-1α,3β,25-triol
**silperisonum**
1-[[p-fluorobenzyl]dimethylsilyl]methylpiperidine

**silperisone**
1-[[4-fluorobenzyl]dimethylsilyl]methylpiperidine

**silpérisone**
1-[[p-fluorobencil]dimetilsilil]metilpiperidina

**sinapultidum**
L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-
\(\text{L-lysine}\)

**sinapultide**
L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-
\(\text{L-lysine}\)

**sinapultida**
L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-
\(\text{L-lysine}\)

**sivelestatum**
o-(p-hydroxybenzenesulfonamido)hippuric acid, pivalate (ester)

**sivelestat**
açido o-(p-hidroxibencenosulfonamido)hipúrico, pivalato (éster)
C$_{20}$H$_{22}$N$_2$O$_7$S

soterenol
2'-hydroxy-5'-(1-hydroxy-2-(isopropylamino)ethyl)methanesulfonamide

N-[2-hydroxy-5-[(1RS)-1-hydroxy-2-{(1R)-1-methyl-2-isopropylaminomethyl}ethan-2-yl]phenyl]methanesulfonamide

soterenol
2'-hidroxi-5'-(1-hidroxi-2-isopropilaminoetil) metanosulfonilida
C$_{12}$H$_{20}$N$_2$O$_4$S

sulmazolum
sulmazole
2-[2-methoxy-4-(methylsulfinyl)phenyl]-3H-imidazo[4,5-b]pyridine

2-[2-méthoxy-4-((méthylsulfinyl)phényl]-3H-imidazo[4,5-b]pyridine

sulmazol
2-[2-metoxi-4-(metilsulfinil)fenil]-3H-imidazo[4,5-b]piridina
C$_{14}$H$_{13}$N$_3$O$_2$S

sunepitronum
sunepitron
N-[[7S,9aS]-octahydro-2-(2-pyrimidinyl)-2H-pyrido[1,2-a]pyrazin-7-yl]methyl]succinimide

sunépitron
1-[[7S,9aS]-2-(pyrimidin-2-yl)octahydro-2H-pyrido[1,2-a]pyrazin-7-yl]methyl[1]pyrrolidine-2,5-dione

sunepitron
N-[[7S,9aS]-octahydro-2-(2-pirimidinil)-2H-piridolo[1,2-a]prazin-7-yl]methyl]succinimida
tecnecio (\textsuperscript{99m}Tc) apcitida

sodium hydrogen [N-(mercaptoacetyl)-\text{-}\text{-}\text{-}tyrosyl-S-(3-aminopropyl)-L-cysteinylglycyl-S-(acetamidomethyl)-L-cysteinylglycyl-S-(acetylamino)methyl]-L-cysteinylglycyl-S-(acetylamino)methyl]-L-cysteinylglycyl-L-aspartyl-L-cysteinylglycylglycyl-S-(acetamidomethyl)-L-cysteinylglycylglycyl-L-cysteinamide cyclic (1-5)-sulfidato(5-)-N\textsubscript{11}, N\textsubscript{12}, N\textsubscript{13}, S\textsubscript{13} oxo][\textsuperscript{99m}Tc]technetate(V)

tecnétium (\textsuperscript{99m}Tc) apcitide

hydrogéno (1-5)-(sulfure cyclique) du \{N-(sulfanylacétyl)-\text{-}\text{-}\text{-}tyrosyl\}{S-(3-aminopropyl)-\text{-}\text{-}\text{-}cystéinylniglicyl-L-aspartyl-L-cystéinylglycylglycylglycyl}[S-(acetamidométhyl)-L-cystéinylglycyl-S-(acetamidométhyl)-L-cystéinylglycylglycyl-L-cystéinamidato(5-)-N\textsubscript{11}, N\textsubscript{12}, N\textsubscript{13}, S\textsubscript{13} oxo][\textsuperscript{99m}Tc]tecnétate(V) de sodium

temocaprilatum

(+)-(2S,6R)-6-\{(15)-1-carboxy-3-phenylpropyl\}amino|tetrahydro-5-oxo-2-(2-thienyl)-1,4-thiazepine-4(5H)-acetic acid

temocaprilat

(+)-acido 2-\{(2S,6R)-6-\{(15)-1-carboxy-3-phenylpropyl\}amino\}-5-oxo-2-(2-thienyl)-1,4-thiazepine-4(5H)-yácido

temocaprilato

ácido (+)-(2S,6R)-6-\{(15)-1-carboxy-3-phenylpropyl\}amino|tetrahydro-5-oxo-2-(2-benzil)-1,4-thiazepine-4(5H)-aceto
**C21H24N2O5S2**

\[
\text{HO}_2\text{C} - \text{H} - \text{N} - \text{CO}_2\text{H}
\]

**thiomersalum**  
**thiomersal**  
**thiomersal**  
**thiomersal**  
2-(éthylmercurisulfanyl)benzoate de sodium

**etilmercurisalicilato de sodio**

**C9H9H9NaO2S**

**thyrotropinum alfa**  
**thyrotropin alfa**  
**thyrotropine alfa**  
**tirotropina alfa**  
thyrotropin (human β-subunit protein moiety), complex with chorionic gonadotropin (human α-subunit protein moiety)

thyrotropine (humaine, partie protéique de 118 aminoacides de la sous-unité β), complexée à la gonadotropine chorionique (humaine, partie protéique de 92 aminoacides de la sous-unité α)

tirotropina (humana, fracción proteica de 118 aminoácidos de la subunidad β), complejado con gonadotropina coriónica (humana, fracción proteica de 92 aminoácidos de la subunidad α)

**C1039H1602N274O307S27**

APDVQDCPEC TLQENPFFESQ PGAFILQCMG CCFSRAYPTP  
LRSKKTLMLVQ KNVTSESTCC YAKSYNVTVT MGGFKVENET  
ACHSTCYYH KS  
FCIPTETYTMH IERRECAYCL TINTTICAGY CNTRDINGKL  
FLPKYAL5QD VCTYRDPIYR TVB1PGCPLK VAPYPSYFVA  
LSCKCGKNT DYSDCIHEAI XTYNCTKPK SYLVCPSV
tifacoginum
N-L-alanylblood-coagulation factor LACI (human clone λ P9 protein moiety reduced)

tifacogine
N-L-alanylfacteur de coagulation sanguine LACI (partie proteique reduite produite par le clone humain λ P9)

tifacogina
N-L-alanilfactor de coagulación sanguínea LACI (fracción proteica reducida producida por el clón humano λ P9)

C_{1400}H_{2167}N_{395}O_{422}S_{23}

tobicillumin
(+)-α-hydroxy-m-tolyl (2S,5R,6R)-3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, isobutyrate (ester)

C_{27}H_{30}N_{2}O_{6}S
trastuzumab

immunoglobulin G1 (human-mouse monoclonal rhuMab HER2 γ1 chain anti-human p185c-erbB2 receptor), disulfide with human-mouse monoclonal rhuMab HER2 light chain, dimer

trastuzumab

immunoglobuline G1 (chaîne γ1 de l'anticorps monoclonal de souris humanisé rhuMab HER2 dirigé contre le récepteur humain p185c-erbB2), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris humanisé rhuMab HER2

trastuzumab

immunoglobulina G1 (cadena γ1 del anticuerpo monoclonal humanizado de ratón rhuMab HER2 dirigido contra el receptor humano p185c-erbB2), dimero del disulfuro con la cadena ligera del anticuerpo monoclonal humanizado de ratón rhuMab HER2

1-453-glycoprotein ICAM 1 (human reduced)

glycoprotéine comprenant 453 amino-acides, constituée du domaine extracellulaire de la molécule d'adhésion intracellulaire-1 humaine (ICAM-1), obtenue par génie génétique

1-453-glicoproteína ICAM 1 (humana reducida)

tremacamrum

tremacamra

QTSVPSXVI LPRGSVVLVT CSTSCGPXKL LGKDPDXK
ELLURSNNK VYELSNGND SQRPCYSCRP KGQSTPEL
TVYWTPERVE LAPLPSQYQV GKNLTLRCQV KGAPRLNT
VVLILREQKL KREPAVGEFA BVTTVLVRTR DHIHGNSR
TELDDLQQLL ELFENTSAPY QLQTFVLPAT PRQLVSPRVL
EVDQTQCTVVC SLQGLPPVSE AQVILLALCO RLPNTVYCN
DGSSAKAVXS VTAEBOCTQR LRCANLGNQ SQFQLQTVIT
YSFPAPNVIL TKPBVEGKTE TVTKCAHHR AKVTLNVGFA
QPLGPRACL LKATPDEBR FSFSCAOELV AGQDLZKQNT
RELAVLYGPR LLDEDCFQMN TNPBSNSQTG MCQAMNLPD
BLKLKLQGTF ELVIGESTVT TRDLGKTYL RARSTQGEBT
REVTVNULSP RYE

valganciclovirum

valganciclovir

L-valine, ester with 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine

valganciclovir

(2S)-2-amino-3-methylbutanoate de (2RS)-2-[(2-amino-6-oxo-1,6-dihydro-9H-purin-3-yl) méthoxy]-3-hydroxypropyle

valganciclovir

L-valinato de 9-[[2-hidroxi-1-(hidroxi metil)etoxi]metil]guanina
xaliprodenum  
xaliproden  
xaliprodén  
xaliprodano

1,2,3,6-tetrahydro-1-[2-(2-naphthyl)ethyl]-4-(a,a,a-trifluoro-m-tolyl)pyridine

ziconotidum  
ziconotide  
ziconotide


ziconotidum  
ziconotide  
ziconotide

Recommended International Nonproprietary Names (Rec. INN): List 4

p. 103 chlorprothixenum
chlorprothixene

replace the chemical name by the following:
(Z)-3-(2-chloro-9H-thioxanthen-9-ylidene)-N,N-dimethylpropan-1-amine

p. 114 chlorprothixenum
chlorprothixène

remplacer le nom chimique par:
(Z)-3-(2-chloro-9H-thioxanthén-9-ylidène)-N,N-diméthylpropan-1-amine

p. 154 chlorprothixenum
clorprothixeno

sustituyase el nombre químico por:
(Z)-3-(2-cloro-9H-tioxanten-9-ilideno)-N,N-dimetilpropan-1-amine

Recommended International Nonproprietary Names (Rec. INN): List 5
(WHO Chronicle, Vol. 19, Nos. 4, 5, 6, 1965)

p. 9 galantaminum
galantamine

replace the chemical name by the following:
(4aS,6S,8aS)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro
[3a,3,2-ef][2] benzazepin-6-ol

Denominations communes internationales recommandées (DCI Rec.): Liste 5
(Chronique OMS, Vol. 19, Nos. 4, 5, 6 1965)

p. 10 galantaminum
galantamine

remplacer le nom chimique par le suivant:
(4aS,6S,8aS)-4a,5,9,10,11,12-hexahydro-3-méthoxy-11-méthyl-6H-benzofuro
[3a,3,2-ef][2] benzazépine-6-ol

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 5
(Crónica de la OMS, Vol. 20, No. 6, 1966)

p. 259 galantaminum
galantamina

sustituyase el nombre químico por el siguiente
(4aS,6S,8aS)-4a,5,9,10,11,12-hexahydro-3-metoxi-11-metil-6H-benzofuro
[3a,3,2-ef][2] benzazepina-6-ol

205
nadroparin calcium

replace the definition by the following:

Calcium salt of a low molecular mass heparin obtained by nitrous acid depolymerization of heparin from pork intestinal mucosa, followed by fractionation to eliminate selectively most of the chains with a molecular mass lower than 2000; the majority of the components have a 2-O-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-O-sulfo-2,5-anhydro-α-mannitol structure at the reducing end of their chain; the mass-average molecular mass ranges between 3600 and 5000 with a characteristic value of about 4300; the degree of sulfatation is about 2.1 per disaccharidic unit.

nadroparine calcique

remplacer la description par la suivante:

Sel calcique d’une héparine de basse masse moléculaire obtenue par dépolymerisation, au moyen d’acide nitreux, d’héparine de muqueuse intestinale de porc; la majorité des composants de la nadroparine sodique possèdent une structure acide 2-O-sulfo-α-L-idopyranosuronique à l’extrémité non réductrice de leur chaîne et une structure 6-O-sulfo-2,5-anhydro-α-mannitol à l’extrémité réductrice de leur chaîne; la masse moléculaire relative moyenne est de 3600 à 5000, avec une valeur caractéristique de 4300 environ; le degré de sulfatation est 2.1 environ par unité disaccharidique.

nadroparina cálcica

sustituya la descripción por la siguiente:

Sal cálcica de una heparina de baja masa molecular obtenida por despolimerización con ácido nitroso de la heparina de la mucosa intestinal de cerdo seguida de fraccionamiento a fin de eliminar selectivamente la mayor parte de las cadenas de masa molecular inferior a 2000; la mayoría de los componentes tienen una estructura de ácido 2-O-sulfo-α-L-idopiranosurónico en el extremo no reductor y una estructura de 6-O-sulfo-2,5-anhidro-α-mannitol en el extremo reductor de la cadena; la masa molecular relativa media es de 3600 a 5000, con un valor característico de 4300 aproximadamente; el grado de sulfatación es de 2.1 por unidad de disacárido.
Recommended International Nonproprietary Names (Rec. INN): List 35
Dénominations communes internationales recommandées (DCI Rec.): Liste 35
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 35

(WHO Drug Information, Vol. 9, No. 3, 1995)

p. 8  delete/supprimer/suppr. mase  insert/insérer/insérezese

dacliximabum  daclizumabum

dacliximac  daclizumab

dacliximac  daclizumab

dacliximab  daclizumab

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 38
(WHO Drug Information, Vol. 11, No. 3, 1997)

p. 174  supprimase  Insérezese

omiloxetino  omiloxetina

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.