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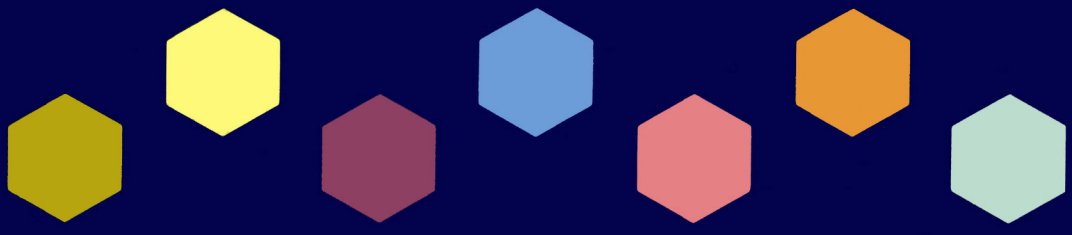
RECOMMENDED INN LIST 54
INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES



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Personal Perspectives

Unfinished business: clinical pharmacology and world health

Clinical pharmacology has existed for just over 40 years and is a relative newcomer to the range of clinical specialties. It took its origins from the development of methods for the formal testing of new medicines in man – especially the randomized, controlled, clinical trial – and from the major concerns about safety of medicines catalysed particularly by the thalidomide disaster of the early 1960s [9]. Essentially, it is the scientific study of medicines in man and has developed its own methodological approaches ranging from single dose studies of medicines in individuals and small groups to wider studies of medicines use in whole populations. Among several enabling branches of the discipline are pharmacovigilance (the monitoring and study of the safety of medicines), pharmacokinetics, drug metabolism, pharmacoepidemiology and more recently, pharmacoeconomics. Many collaborative partnerships have been forged with pharmacists, analytical chemists, statisticians, other clinicians and, more recently, epidemiologists and health economists, in developing these themes.

As a new discipline clinical pharmacology has had to fight for recognition, both in medical schools but also in the wider world of health care delivery. This is perhaps surprising when one of the main tasks of any physician is the safe and effective prescription of medicines, and of any health service to ensure the availability of medicines of high quality, safety and efficacy to be used in the most cost-effective manner. (Costs of medicines may be 10% of total healthcare spending in the public system in developed countries but for many developing countries often exceed 30% of health budget.) However, the demand for a new lecturer in molecular biology in a medical school, a new cardiologist in a teaching hospital or a further administrator in a health service commonly takes precedence over creating a position for a clinical pharmacologist.

If clinical pharmacology has had some difficulties in making its presence felt in the developed world, these have been much greater in developing world countries where medical needs are often comparatively much greater but available, trained personnel are few.

Against this background, recently revised "Aims and Functions of the International Union of Basic and Clinical Pharmacology (2) include . . . "helping in all ways the development of pharmacology throughout the world particularly in emerging countries". The aims include "(to) improve and harmonize the teaching of rational use of drugs . . . particularly in developing countries" and "(to) improve the utilization of clinical pharmacological services in health care delivery, particularly in developing countries. . ."

Developing–developed world collaboration in clinical pharmacology

Distance and the lack of easy communication militated against collaborative work between developed and developing countries for many years. An exception was the work of D.R. Laurence, a pioneer clinical pharmacologist from the United Kingdom who worked over several years with colleagues from Bombay (now Mumbai), India to determine the safe and effective dose of tetanus antitoxin for the treatment of this (now largely preventable) disease. Their conclusions in 1968 were that "in the treatment of tetanus 10 000 IU (international units) of equine antitoxin is about as effective as 200 000 IU" [14].

Remarkably, this was the first systematic attempt to define a rational dose of antitoxin but it also established that inter-country collaborations on

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Article adapted from the IUPHAR Clinical Pharmacology lecture of the same title given at the 8th World Congress of Clinical Pharmacology and Therapeutics, Brisbane, Australia, August 2004. It appeared in: International Journal of Risk & Safety in Medicine, ***17****: 65–71 (2005) authored by Anthony J. Smith, Department of Clinical Pharmacology, University of Newcastle and WHO Collaborating Centre for Training in Pharmaco-economics and Rational Pharmacotherapy, Australia.*

matters of importance to public health were possible and could yield answers which reduced the cost of provision of services in the public sector, in this case by a factor of 20.

In the late 1960s and throughout the 1970s a trickle of young trainees from developing countries was funded to work in clinical pharmacology units in Europe and the USA. In retrospect, the unawareness of many of the host departments of the needs of the developing country, and the immaturity of the discipline itself often meant that their training was not tailored to real needs. For instance, acquiring skills in the measurement of small amounts of medicines in blood samples was not relevant for a trainee going back to a country which had difficulty in providing even essential medicines to the poorest of its people let alone setting up a sophisticated analytical facility in which the trainee could practice his new-found techniques. This lack of congruence between training and career prospects often led to disillusion and migration of the trainee either back to the laboratories of the developed world or into a different clinical specialty at home.

The advent of the Internet coupled with easier travel has transformed the possibilities for collaboration between developed and developing countries and there are many examples of partnerships producing important research findings of direct benefit to both partners. Malaria remains one of the most perplexing tropical diseases and the long-standing collaboration between Oxford University and the research group in Mahidol University in Thailand is a good example of a better approach to research into issues of safe and effective treatment [16]. A simple but relevant study of the efficacy and safety of rectal artesunate compared with quinine in the same disease published in 2004 was conducted by a team including clinical pharmacologists from both developed and developing African countries [3]. Increasingly, research collaboration is occurring between African and Asian centres and clinical pharmacologists in developed countries, particularly relating to malaria but also to other tropical diseases.

The benefits of collaboration are by no means one-way and the placebo-controlled trial finally confirming the value of magnesium sulphate treatment in pre-eclampsia could only have recruited its 10 000 patients over a short time period by working collaboratively with clinicians and clinical pharmacologists in several developing countries. The results are applicable to both developed and developing communities [1].

Clinical toxicology has often been a neglected area of research. Here again recent inter-country collaborations have advanced knowledge – for example, the Oxford–Colombo research unit working on the management of poisoning both with organophosphate insecticides (estimated to kill 200 000 people worldwide each year) and with Oleander species – plants often taken with suicidal intent in Sri Lanka and containing glycosides with a digoxin-like cardiotoxic effect which, untreated, may be rapidly fatal [7].

Recently several centres of clinical pharmacology have developed collaborative programs concentrating on training in rational medicines use. Examples include the current Egypt–Denmark–Sweden collaboration on rational prescribing and Spanish initiatives linking clinical pharmacology training into the health care systems of Central and South American countries.

Applying research lessons to the use of medicines in the health care system

Are the newly-won lessons coming from the developed-developing research partnerships having an impact on health services? The evidence obtained is “necessary but not sufficient” to ensure its translation into health policy and delivery of health care but there are pointers to ways in which this might be done.

Experience gained in Australia over the past 13 years shows that the role of the clinical pharmacologist can be a central one in helping translate the scientific evidence into health care practice. The new feature that has brought these together is the creation and implementation of a National Medicines Policy (NMP) based on the prototype of the World Health Organization (WHO) [19]. Many of the ingredients of a NMP have existed in Australia for many years. Quality, safety and efficacy of new medicines are regulated by the Therapeutic Goods Administration while equity of access to medicines is assured by the subsidies provided by central government and administered by the Pharmaceutical Benefits Scheme. Both of these have been in place for over 50 years. However, after much lobbying, particularly by consumer organisations and in line with WHO guidelines, Quality Use of

Medicines was adopted by government as an additional component of the policy in the early 1990s.

The committee appointed to have oversight of this new policy direction conducted research into local and overseas practice, sponsored new investigation and tested interventions where necessary. By 1995, it was in a position to collate the evidence about improving the quality of use of medicines into a document suitable as a blueprint for intervention on a national scale. In 1997, the, then, Minister for Health announced funding for a National Prescribing Service (NPS) to implement these strategies and evaluate their impact. The NPS was set up as an independent company receiving its funds from government but independent from it in all other respects. It has implemented many interventions over the past 6 years with evidence of benefit in terms of the more rational use of medicines – especially antibiotics [15]. Within this national enterprise most of the country's clinical pharmacologists (almost all of them on the staff of University Medical Schools) have found important and relevant roles. In this, the translation of research findings into the delivery of health care services can be clearly seen and the role of the clinical pharmacologist defined. The Australian NMP was revised and published in its present form in 2000 [2].

Advocacy at a political level

Most health departments in developing countries have little or no contact with clinical pharmacology and rely very heavily for advice about pharmaceuticals on pharmacists who have worked in the bureaucracy often for many years. Many have given great service but few have a clinical dimension to their experience and therefore are often unaware of emerging research evidence about medicines and commonly are not in constant touch with practitioners working in the hospital or community. A clinical pharmacologist can provide the link between government and the health care community and can also be a powerful advocate for the introduction of new services (e.g., the systematic collection of data about adverse reactions to medicines or the strengthening of prescribing education in a medical school curriculum). Politicians without a health training are not aware of the distinctive role that clinical pharmacology can have and fail to recognize the discipline as separate from "pharmacology" or "pharmacy".

Lack of recognition means clinical pharmacologists commonly are not regarded as full specialists. This, in turn, carries the implication of poorer overall salaries, often no right of private practice and a poorly formulated job description. Recruitment into clinical pharmacology is adversely affected by this, and young people who might contribute to the overall goal of improving drug use understandably opt for the safer clinical specialties. There is an urgent need for advocacy at government level to redress these perceptions and demonstrate the value of clinical pharmacology to any health care system.

Development of national medicines policies

A national policy provides a blueprint for the future, can be divided into discrete areas which can be allocated to the most appropriate groups to implement and also stands as a document against which progress can be measured. Governments change and new ones may sometimes abolish policies made by their predecessors. This is unlikely to happen if the policy commands general support within the health care professions and, especially, from consumers. Ideally a policy should be developed with input from all those with a stake in it. This implies inclusion of members of the government and its officers, health professionals including pharmacists, nurses, clinical pharmacologists and other and medical practitioners and, wherever possible, representatives of consumer organizations. A well supported and agreed policy will have fewer problems in its implementation stage.

Implementing policy

There are many tasks under this one heading. Among them are compiling evidence-based essential medicine lists and standard treatment guidelines and providing objective, relevant medicines information as most health professionals in developing countries rely almost entirely on the pharmaceutical industry for their information.

Perhaps one of the most relevant tasks in the present climate of heightened concern about safe use of medicines is the development of systems for the detection and monitoring of adverse reactions and of a process that can respond to these in a timely manner. [Some developing countries have an extra concern about medicines available to consumers as up to 25% may be counterfeit, containing none of the active product, or at best a reduced amount [20]. While not technically recognized as such, failure to improve

due to lack of the expected ingredients in a medicine might well be classified as an adverse response.]

However, even a fully developed monitoring system will not detect all the safety issues relating to prescribed medicines and formal studies are often required. As an example, a detailed study of safety in Australian hospitals [17] published in 1995 found that 16.6% of hospital patients, in a random survey of 14 179, had some form of adverse event. Of these almost 11% were related to medication. Further analysis showed that the elderly were most at risk, poor prescribing practice contributed and that failure to monitor the consequences of medicines administration was the commonest direct cause of the adverse event. More than 80% of the adverse events were judged to be preventable [4]. A later overview of 14 published Australian studies [11] confirmed that between 2.4 and 3.6% of all hospital admissions were reported to be medicine-related with the highest proportion (15–22%) in the elderly. Thus, we have sufficient evidence about incidence and factors influencing adverse response to provide a basis for intervention – currently being undertaken at a national level by, among others, the Australian Council for Safety and Quality in Health Care [12].

While WHO has recently identified patient safety as a global priority and in 2004 launched the Word Alliance for Patient Safety [6], there are many developing countries in which fundamental data gathering, let alone formal studies, for the detection of adverse response to medicines is yet to be established. The WHO Collaborating Centre in Uppsala, which carries the responsibility for International Drug Monitoring, receives data about adverse response to medicines from only 73 countries (annual report 2003–2004 [13]) with a further 13 currently trying to develop their data systems to the point of compatibility with the Centre's requirements. As more than 150 countries worldwide now have national medicines policies it appears that the safety aspect of these policies has not yet received the priority it deserves.

Paradoxically, it can be predicted that for many developing countries there is some safety protection in relying on an Essential Medicines List for supply of medicines as these lists commonly contain older, better known medicines whose adverse effect profile is well established. There is therefore the small consolation of less concern about newer medicines whose safety has become a concern only after wider use in developed countries and which have subsequently been withdrawn from the market.

The clinical pharmacologist should also have a role in the development and implementation of drug regulatory systems, and (particularly, but not exclusively, in poorer countries) for the cost-effective purchase of medicines, as the comparative performance of medicines in clinical use is the basis for deciding which is the most cost-effective and therefore most suitable for inclusion in a national formulary or a list of subsidised medicines.

For many developing countries herbal and other complementary medicines are first-line medications. For many of these the evidence of safety and efficacy falls below the standards that would be expected of prescription medicines. This is an important area for local research which must include relevant clinical trials.

Finally, but probably as important as any other aspect of national policy, is the centrality of good education about prescribing. An average prescriber writes over 250 000 prescriptions in a practising lifetime – some write many more – yet the quality of prescribing leaves much to be desired in both developed and developing countries. For many medical schools pharmacology and even clinical pharmacology teaching are well established but the extra step which translates theoretical knowledge into the practical skills of prescribing does not feature in the curriculum and graduates are left to "pick up" prescribing once they are exposed to the realities of everyday practice. There is now a well evaluated WHO programme [5,18] which adopts a problem-based approach to selection of medicines for prescription and encourages the student to build a personal, evidence-based formulary. Teachers have found it valuable and young graduates who have been through the course have a much greater confidence in their abilities both to prescribe and to maintain their formulary current as new medicines are introduced or older ones removed. In Australia the course has been adapted for computer-interactive learning and is being used in most medical schools [10].

Thanks to work conducted by many concerned people in both developed and developing countries there is now an adequate body of evidence about interventions that work (and those that do not) to enable any country to improve the use of

medicines. An article outlining these interventions states “Sufficient evidence is now available to persuade policy makers that it is possible to promote rational drug use. If such effective strategies are followed the quality of health care can be improved and drug expenditure reduced” [8].

Implications for the developing world: training and employment of clinical pharmacologists

The list of tasks generated around a national medicines policy gives an idea of the newer roles being taken on by clinical pharmacologists, often working from an academic base, as key members of the teams required to put in place strategies to improve the quality of use of medicines. However, the list also suggests the training and skills base required by any clinical pharmacologist who becomes involved in this process. The newer roles do not make conventional postgraduate training in the discipline irrelevant but additional skills and knowledge are needed for the new tasks.

Some clinical pharmacology departments do have sufficient involvement in national policies to be able to provide the necessary hands-on practical training but too many do not. If the supplementary training is to be made available there is need for a focus on both recruitment of trainees and provision of suitable training.

This seems to be an ideal opportunity for an alliance between IUPHAR (and particularly its Clinical Pharmacology Division, with its stated aims of improving the reach of the discipline into health care delivery) and WHO with its concerns for the appropriate, safe and effective use of high quality medicines in all countries, and not solely in the richer parts of the world. Out of such an alliance might emerge a new training programme, perhaps a “fellowship” scheme for trainees, with guarantees from their home governments of a career path at completion of training. Some ongoing links between the trainees and their mentors would be appropriate and the training itself could be carried out both in the home country and, for part of the time where needed, in an overseas training institution. With the increasing use of computer-based instruction and interaction the previous problems with communication should be easily overcome. Donor support would be needed. There are some donors for whom this sort of program would be attractive and consistent with other areas related to rational use of medicines which they have already supported. In this way it might be possible to harness the potential for clinical pharmacology to make its full, and currently under-exploited contribution to the improvement of world health.

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Safety and Efficacy Issues

Transdermal fentanyl: abuse by adolescents

Canada — Fentanyl transdermal system (Duragesic®) has been marketed in Canada since 1992 and is indicated for the management of chronic pain in patients requiring continuous opioid analgesia for pain that is not optimally managed with weak or short-acting opioids (1). Opioid-naive patients may be at risk of overdose with the use of opioid drugs, including fentanyl.

From 1998 to 2005, Health Canada received 4 reports of abuse of fentanyl patches by adolescent boys aged 14–17 years. Three of the boys died, and 1 had not recovered at the time of reporting. The patches were found either in home medicine cabinets or were prescribed to a parent. In 3 cases the use of marihuana was reported.

From 28% to 84% of the active ingredient may be recovered from a fentanyl transdermal system even after 3 days of therapeutic use, which is more than sufficient drug for potential abuse (2) The fentanyl from the patch can be abused by ingestion, intravenous injection, volatilization and inhalation, or application of multiple patches, and such abuse may result in death (3–5). Potential for overdose also exists when heating pads are applied to the skin to raise skin temperature and increase the rate of fentanyl absorption from the patch (6, 7). In addition, low concentrations of fentanyl are sufficient to induce respiratory depression (8).

Abuse of fentanyl patches depends on access to improperly discarded or secured patches. The Canadian product monograph provides recommendations for the safe disposal of patches. Specific information for the patient details the risks of fentanyl and how to apply, remove and dispose of the transdermal patches (1). Safe and secure dispensing, storage and disposal measures must be reinforced for patients, pharmacists and physicians.

Extracted from Canadian Adverse Reaction Newsletter, Volume 15 (3), July 2005.

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Safety of fentanyl transdermal patches

United States of America — The Food and Drug Administration (FDA) is investigating reports of death and other serious side effects from overdoses of fentanyl in patients using fentanyl transdermal (skin) patches for pain control. Deaths and overdoses have occurred in patients using both the brand name product Duragesic® and the generic product. The directions for using the fentanyl skin patch must be followed exactly to prevent death or other serious side effects from overdosing with fentanyl.

Because fentanyl skin patches are very strong narcotic (opioid) painkillers that may cause death from overdose, they should always be prescribed

at the lowest dose needed for pain relief. Fentanyl skin patches should not be used to treat short-term pain, pain that is not constant, or for pain after an operation. They should only be used by patients who are opioid tolerant, or who have chronic pain that is not well controlled with shorter-acting painkillers.

Reference: FDA Public Health advisory http://www.fda.gov/medwatch/SAFETY/2005/duragesic_ddl.pdf

Rosiglitazone: decreased high-density lipoprotein cholesterol

Canada — Rosiglitazone (Avandia®) is a member of the thiazolidinedione family of oral hypoglycaemic agents used to improve glycaemic control by increasing insulin sensitivity in muscle and adipose tissue and inhibiting hepatic gluconeogenesis (1). It has been marketed in Canada since March 2000.

Clinical trials using rosiglitazone as monotherapy detected increases in levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) and decreases in levels of free fatty acids (1). Decreased HDL-C levels were not seen in over 1400 patients treated with rosiglitazone in clinical trials (2). It is noteworthy that fibrates generally have a beneficial effect on HDL-C and triglyceride levels but occasionally have been associated with decreases in HDL-C and apolipoprotein A-I concentrations (2).

From 2000, to 2004, Health Canada received one report of a decreased HDL-C level suspected of being associated with rosiglitazone. The abnormal lipid values resolved 2 months after stopping rosiglitazone therapy. Subsequently, the patient developed symptoms of angina and underwent angioplasty. The medical literature describes 3 cases of profound decreases in HDL-C and apolipoprotein A-I concentrations during treatment with rosiglitazone (2). Triglyceride levels also increased during treatment. In all 3 cases, the HDL-C level increased after withdrawal of the rosiglitazone. Two patients were taking a fibrate but did not have a decreased HDL-C level until rosiglitazone was introduced.

Given the findings of the 3 cases from the medical literature and the Canadian case, it would be advisable to measure baseline HDL-C and triglyceride levels in patients prescribed rosiglitazone and check them again shortly after the start of therapy.

Extracted from Canadian Adverse Reaction Newsletter, Volume 15 (3), July 2005.

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Ibuprofen: Stevens–Johnson syndrome

Canada — Stevens-Johnson syndrome (SJS) is a severe blistering rash affecting both skin and mucous membranes. The majority of cases have been attributed to drug exposures (1, 2). The reaction begins with burning and painful lesions on the face and upper torso and extends to the rest of the body. Blistering and epidermal detachment may occur (1–3). Patients may present with fever, malaise, myalgia and ocular manifestations. Mortality has been estimated at 5% of cases (3, 4).

From 1973, to 2005, Health Canada received 4 reports of SJS suspected of being associated with ibuprofen. At the time of reporting, 3 patients had not recovered, and the outcome was unknown for 1 patient. The reports involved patients aged 13 to 34 years and were all received after April 2001. The dosages ranged from 200 mg to 1200 mg daily. The onset of reactions varied from the day of administration to approximately 15 days after starting ibuprofen. In one report, carbamazepine was indicated as a suspect drug along with ibuprofen.

Ibuprofen has been available over the counter since August 1989. SJS is listed in the product monographs for ibuprofen products (5, 6). Although cases of SJS remain rare, patients taking ibuprofen should be warned to discontinue use and seek medical attention should any rash, fever without an alternative explanation or mucosal symptoms develop (2).

Extracted from Canadian Adverse Reaction Newsletter, Volume 15 (3), July 2005.

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Stringent conditions for COX–2 Inhibitors

New Zealand —The class of medicines known as COX-2 inhibitors will stay on the market, but with considerably stronger warnings for their use and the requirements for pharmaceutical companies to collect and report information on usage. Pharmaceutical companies will also have to provide additional safety information as it becomes available. The Ministry of Health is also seeking to extend, until further notice, the voluntary ban by pharmaceutical companies on promoting these products.

Recommendations made by the Medicines Adverse Reactions Committee (MARC), and accepted by the Ministry of Health, end months of uncertainty for patients. A review of the cardiovascular safety of the COX-2 inhibitors was begun in October 2004 after rofecoxib (Vioxx®), one of six COX-2 inhibitors marketed in New Zealand, was withdrawn after international findings that its use was associated with an increased risk of heart attacks and strokes.

In February 2005, patients at high risk of heart attacks or strokes were warned against using COX-2 inhibitors. However, for some people these medicines are the best treatment option and giving doctors and patients enough information will allow both to weigh up the risks and benefits. Both the Royal Australasian College of Surgeons and the Australian and New Zealand College of Anaesthetists have been advised that it is crucial for their members to carry out a full risk-benefit analysis for all patients, and that they fully inform patients of the risks and benefits before routinely using COX-2 inhibitors for relief of pain and inflammation associated with an operation.

Medsafe and the University of Otago Pharmacovigilance Centre will be monitoring these products. MARC has recommended prohibiting direct-to-consumer advertising of COX-2 inhibitors, and there has been a voluntary moratorium in place since December 2004.

COX-2 inhibitors available in New Zealand:

Celecoxib (Celebrex®)
Etoricoxib (Arcoxia®)
Meloxicam (Mobic®)
Parecoxib (Dynastat®)

[Valdecoxib (Bextra®) was voluntarily withdrawn April 2005.]

Reference: Media Release. Stringent Conditions for COX-2 Inhibitors, 29 April 2005 on http://www.medsafe.gov.nz

Sildenafil, tadalafil and vardenafil: eye problems reported

United States of America — The Food and Drug Administration (FDA) has approved updated labelling for tadalafil (Cialis®), vardenafil (Levitra®) and sildenafil (Viagra®) to reflect a small number of post-marketing reports of sudden vision loss, attributed to NAION (non arteritic ischemic optic neuropathy), a condition where blood flow is blocked to the optic nerve.

FDA advises patients to stop taking these medicines and contact a doctor or healthcare provider immediately if they experience sudden or decreased vision loss in one or both eyes. Further, patients taking or considering taking these products should inform their health care professionals if they have ever had severe loss of vision, which might reflect a prior episode of NAION. Such patients are at an increased risk of developing NAION again.

At this time, it is not possible to determine whether these oral medicines for erectile dysfunction were the cause of the loss of eyesight or whether the problem is related to other factors such as high blood pressure or diabetes, or to a combination of these problems. The new labelling information is available along with additional information for healthcare providers and consumers online at:

Viagra (http://www.fda.gov/cder/consumerinfo/viagra/vIAGRA.htm)

Levitra (http://www.fda.gov/cder/drug/infopage/vardenafil/default.htm)

Cialis (http://www.fda.gov/cder/drug/infopage/cialis/default.htm)

Reference: *FDA Statement*, 8 July 2005 on http://www.fda.gov

Nesiritide: safety report and measures

United States of America — The Food and Drug Administration has posted the recommendations of an expert panel of cardiology and heart failure clinicians with regard to nesiritide (Natrecor®), the first member of a new drug class, human B-type natriuretic peptide (hBNP) manufactured from *E coli* using recombinant DNA technology.

Nesiritide was approved in 2001 for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnoea at rest or with minimal activity. Two recent publications have raised questions about the safety of nesiritide with respect to worsening renal function and death. A Nesiritide Advisory Panel was convened and has published a report with the following observations.

Renal dysfunction
The use of nesiritide has been associated with a dose-dependent increase in serum creatinine indicating renal dysfunction at doses described in the package insert, including the dose recommended for initiation of treatment. Most of these increases occurred days after discontinuation of the drug. The mechanism of these creatinine changes, their duration, implications for survival, longer term renal function and other clinical consequences is not clear. There is no evidence, however, that nesiritide results in improvement in renal function.

Studies to clarify the mechanism and reversibility of the observed changes in creatinine should be undertaken. Additional analyses of existing data to identify the characteristics of patients who experience creatinine elevation should be conducted.

Mortality
Completed trials show that the use of nesiritide was associated with a trend toward an increase in mortality rate at 30 days, with a hazard ratio of approximately 1.3, a 30% increase. No increased hazard is observed at 180 days. Because of the small numbers of events in the current database and the inconclusive nature of these findings, the panel recommends that additional studies be conducted to assess the effect of nesiritide on survival.

Clinical trials
The panel strongly recommended continued enrolment in ongoing trials of nesiritide, as well as enrolment in trials that are soon to commence. This includes a plan to conduct a large (several thousand subjects) trial of clinical outcomes to assess further the benefits and risks of nesiritide compared to standard therapy.

Further exploration of the data from the completed trials should be carried out to examine the effects of nesiritide in subgroups of patients.

Recommendations
The use of nesiritide should be strictly limited to patients presenting to the hospital with acutely decompensated congestive heart failure who have dyspnoea at rest.

Nesiritide should **not** be used to replace diuretics. Furthermore, nesiritide should **not** be used:

- for intermittent outpatient infusion
- for scheduled repetitive use
- to improve renal function, or
- to enhance diuresis.

The sponsor should immediately undertake a proactive educational program to inform physicians regarding the conditions and circumstances in which nesiritide should and should not be used.

Reference: 2005 Safety Alert and The Panel's report, 13 July 2005 on http://www.fda.gov/medwatch

Mifepristone, sepsis and blood infection

United States of America — The Food and Drug Administration (FDA) is investigating serious adverse events associated with mifepristone (Mifeprex®) and highlighting the risk of sepsis or blood infection when undergoing medical abortion using mifepristone and misoprostol in a manner not consistent with the approved labelling. There are now four cases of deaths from infection between September 2003 to June 2005 following medical abortion with these drugs.

The bacteria thought to have caused the fatal infections have been identified in two of the cases and the other two cases are under investigation by FDA together with the Centers for Disease Control and Prevention, State and local health departments, and the manufacturer of Mifeprex®. Doctors are urged to have a higher level of suspicion for sepsis in patients. Previously, the FDA has received reports of serious bacterial infection, bleeding, and ectopic pregnancies that have ruptured, and death. Those reports led to the revision of the black box labelling.

Reference: *FDA News*, P05-43 19 July 2005 on http://www.fda.gov/cder/drug/infopage/mifepristone/default.htm.

Mifepristone: revised safety information

Switzerland — The Health Authority, Swissmedic, has released new information for health professionals concerning rare complications of sepsis and haemorrhage reported from USA and Canada following use of mifepristone (Mifegyne®) and misoprostol.

Mifepristone and misoprostol are licensed in Switzerland for medical abortion up to 49 days amenorrhoea. Recommended dosages are oral mifepristone 600 mg followed 36 to 48 hours later by 400 µg (micrograms) oral misoprostol. The cases of sepsis and haemorrhage reported from USA seem to have followed vaginal administration of misoprostol, which is unauthorized in Switzerland.

In the reported cases no fever was identified, so that it is very important to monitor patients, particularly those suffering from conditions such as tachycardia, hypovolaemia or leucocytosis. The safety information for Mifegyne® was already strengthened in December 2004 to reflect concerns and warn health professionals of these risks.

It should be noted that severe infection and sepsis can occur following abortion with both medical or surgical methods, and infection can also occur following normal and Caesarian delivery.

Reference: Des nouvelles informations sur les complications sous traitement par mifepristone. 22 July 2005. http://www.swissmedic.ch

Suicidality with SSRIs in adults

Australia — In 2004, the Australian Adverse Reactions Advisory Committee (ADRAC) published a statement on the use of SSRI antidepressants in children and adolescents in view of evidence that use of these agents in these age groups was associated with an increased risk of suicidality, including suicidal ideation, suicide attempts and self-harm events (1). SSRIs are not registered for the treatment of depression in those less than 18 years of age, and neither are any other antidepressants.

Recently, ADRAC conducted a review of the evidence of suicidal thoughts and behaviour associated with the use of SSRIs in adults. The SSRI antidepressants included are citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, and the related medicine, venlafaxine. The Committee concluded that, in most adult patients, SSRIs in the treatment of depression are beneficial or cause no harm. However, it was noted that individual case reports, including some describing dechallenge and rechallenge, support an association between SSRI use and new onset suicidality (2, 3). When this syndrome occurred it tended to develop soon after introduction of an SSRI, or an increase in the dose and to be associated with akathisia, agitation, nervousness and anxiety. The effect often persisted with continuing treatment. Similar symptoms can follow withdrawal of the SSRI.

Because of the risk of suicidal ideation and behaviour in both adults and children being treated for major depression and other psychiatric disorders, the TGA has recently required the sponsors of antidepressants, including the SSRIs, to update their Australian product information with appropriate warnings. The warnings provide the following advice:

- Worsening of depressive symptoms and emergence of suicidality may occur with treated or untreated depressive illness;
- Patients should be closely monitored for suicidality in the first weeks of treatment, and if there is a change in dose (up or down);
- Consideration should be given to changing or discontinuing therapy if worsening of symptoms persists or emergence of suicidality occurs with treatment;
- Patients and caregivers should be advised to monitor for worsening illness, suicidal or self-harm-related thoughts and behaviour and advised to seek medical assistance immediately should these occur.

Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 24, Number 4, August 2005

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Ezetimibe and muscle disorders

Australia — Ezetimibe (Ezetrol®) lowers lipids by inhibiting the intestinal absorption of cholesterol and is indicated for the treatment of hypercholesterolaemia. Out of 144 Australian reports received with ezetimibe since registration in June 2003, 44 have been of muscle disorders, including myalgia, muscle cramp, weakness and pain with five reports describing increased serum creatine kinase and three listing symptoms possibly indicative of an allergic reaction.

In premarketing clinical trials, reported rates of myalgia were less than 2% with ezetimibe, 2.4% with statins and 3.2% with ezetimibe coadministered with a statin (1). The association of the lipid-lowering statins (atorvastatin, fluvastatin, pravastatin, simvastatin) with muscle disorders, including rhabdomyolysis, is well-known (2). Although ezetimibe has been associated with muscle disorders, at present it is uncertain whether it can cause rhabdomyolysis, and if so what factors increase the risk (3).

In the 44 cases reported to the Australian Adverse Reactions Advisory Committee (ADRAC) with muscle disorders, the time to onset ranged from hours to approximately 4 months, but in almost half of the cases, the symptoms developed within two weeks. Twenty-one patients had a history of muscle disorder or increased creatine kinase with statins.

Ezetimibe was given concomitantly with a statin in 5 of the 44 cases and in two published cases (4). The details of these cases are consistent with an interaction between the statin and ezetimibe. Typically, the patient had been taking the statin long term, and the symptoms of myalgia or increase in creatine kinase developed within three months of the addition of ezetimibe. Four patients recovered on withdrawal of ezetimibe alone, and another tolerated reintroduction of atorvastatin 80 mg daily without ezetimibe.

Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 24, Number 4, August 2005

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Pathological gambling with cabergoline

Australia — In the past 2 years the Australian Adverse Reactions Advisory Committee (ADRAC) has received 4 reports describing the development of pathological gambling in association with

cabergoline (Cabaser®). These are the only 4 reports of this problem in the ADRAC database. All 4 patients were taking long-term levodopa and the excessive gambling commenced a number of months after cabergoline was added. In 3 of the 4 Australian cases, the patient also developed obsessive, inappropriate or abnormal behaviour. In all cases the gambling and other behavioural problems resolved when cabergoline was stopped.

Pathological gambling has been reported before in association with dopaminergic therapy for Parkinson's disease (1). Almost all of these patients were taking long-term levodopa and some were also taking dopamine receptor agonists such as pergolide and pramipexole. In a number of cases, the appearance of pathological gambling occurred after an increase in dosage of levodopa and/or a dopamine receptor agonist.

It has been proposed that an increase in stimulation of dopaminergic rewards systems is important in the development of pathological gambling and other addictive and compulsive behaviours. This is probably a very rare adverse effect but prescribers should be alert for its occurrence in patients who are taking combinations of levodopa and dopamine receptor agonists.

Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 24, Number 4, August 2005

Reference: Driver-Dunckley E, Samanta J, Stacy M. Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. *Neurology* 2003; **61**: 422-23

Icodextrin peritoneal dialysis solution: falsely elevated blood glucose readings

Singapore — There have been recent adverse reports in Australia, Canada and the United Kingdom of injuries caused by falsely elevated blood glucose readings in diabetic patients who are using peritoneal dialysis solution that contains icodextrin as an ingredient (e.g. Extraneal®) and blood glucose monitoring systems that are based on the glucose dehydrogenase–pyrroloquinolinequinone (GDH-PQQ) method. Although this is a known drug-device interaction, such serious mishaps which could be fatal, continue to be reported overseas. In Singapore, no similar case has been reported.

Icodextrin, a glucose polymer, is broken down into maltose in the body. The accumulation of blood maltose can interact with glucose monitoring systems that are not glucose-specific (e.g. those using the GDH-PQQ method) and give rise to falsely elevated glucose readings. As a result, patients may receive an excessive dose of insulin leading to a hypoglycaemic episode. On the other hand, cases of hypoglycaemia might not be treated if their hypoglycaemic states are masked by glucose readings that are falsely elevated into the normal range.

To reduce the risk of drug-device interaction, the following preventive measures are recommended:

- Diabetic patients who require dialysis and are prescribed Extraneal® should be issued with a Safety Alert Card provided by the manufacturer. Patients should be advised to present this card to any attending medical personnel.

- Patients on Extraneal® should use only glucose-specific meters that are not subjected to interference from icodextrin metabolites. Patients should be given a specific instruction on the appropriate type of home blood glucometer that they should use and to verify the suitability of the glucometers with the companies distributing the meters.

- Patients should be reminded to read the product package information leaflet of the glucose monitoring system before using the product.

Reference: Safety reports. http://www.hsa.gov.sg

New requirements for pseudoephedrine products

United States of America — Pharmacies that engage in over-the-counter sales of tablet forms of products containing ephedrine, pseudoephedrine, or norpseudoephedrine must keep those products behind the pharmacy counter, or in a locked case within 30 feet and in a direct line of sight from a pharmacy counter staffed by an employee of the pharmacy. This law does not apply to liquid, liquid capsule, or liquid-gel capsule forms of the products. There are also new record-keeping requirements when selling one of these products. Before completing the over-the-counter sale of a product containing ephedrine, pseudoephedrine, or norpseudoephedrine, a pharmacy must require the person making the purchase to:

- display a driver's license or other form of identification containing the person's photograph and indicating that the person is 16 years of age or older; and

- sign for the purchase.

The pharmacy must make a record of the sale including:

- the name of the person making the purchase; the date of the purchase; and

- the item and number of grams purchased.

The pharmacy must take actions necessary to prevent a person who makes over-the-counter purchases of one or more products containing ephedrine, pseudoephedrine, or norpseudoephedrine from obtaining more than two packages of those products in a single transaction; or six grams of ephedrine, pseudoephedrine, norpseudoephedrine, or a combination of those substances.

Reference: Texas State Board of Pharmacy, on http://www.tsbp.state.tx.us

Efalizumab: warning of thrombocytopenia

United States of America — The manufacturer of efalizumab (Raptiva®) has informed health care professionals of important new safety information. Efalizumab is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Two cases of haemolytic anaemia were observed in clinical trials of efalizumab and two additional cases were reported in the postmarketing setting. A causal relationship between efalizumab and these events has not been established but cannot be excluded. Based on this data, a warning has been added to the prescribing information.

Reference: Communication from Genentech (http://www.gene.com/gene.contact/) posted on https://www.accessdata.fda.gov/scripts/medwatch/

Antiretrovirals: HIV, hepatic impairment and HBV/HCV

European Union — During 2002, the European Medicines Agency (EMEA) requested the marketing authorisation holders for all licensed antiretroviral medicinal products in Europe to conduct a retrospective review from clinical trials and post marketing data in HIV patients with hepatic impairment and/or HBV/HCV co-infection, with the aim to review pharmacokinetic and safety data, and propose measures to improve the availability of relevant data from these patients.

After an assessment of initial responses in April 2004, marketing authorization holders jointly established the HIV/Hepatitis Co-infection Cohort Collaboration (HIVCO) to plan how to obtain information on the hepatic safety of highly active antiretroviral treatment (HAART) in co-infected patients. At the CHMP and Pharmacovigilance Working party meeting in June 2005, the CHMP endorsed the HIVCO proposal to use the ongoing Study on Data Collection on Adverse Events of Anti-HIV Drugs for the evaluation of liver related death in co-infected patients.

Reference: EMEA public statement. 5 August 2005. EMEA/CHMP/249537/2005 on http://www.emea.eu.int

Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious and unexpected adverse drug reactions. A signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information". All signals must be validated before any regulatory decision can be made.

Herbal Medicines

Monograph for cultivation of herbal antimalarial: *Artemisia annua*

World Health Organization — Recent estimates of the global burden of malaria have shown increasing levels of morbidity and mortality, particularly in Africa. Key among the factors contributing to the increase is the widespread resistance of *Plasmodium falciparum* to conventional antimalarial drugs. Over the past decade, a new group of antimalarial compounds which includes artesunate, artemether and dihydroartemisinin, have been deployed on an increasingly large scale.

Since 2002, WHO has recommended the use of artemisinin-based combined therapy (ACT) for the treatment of falciparum malaria. The world market is now growing very rapidly, and demand for artemisinin is strong. Artemisinin is extracted from the *Artemisia annua* L plant and in order to ensure quality and sustainable supplies, the plant must be cultivated following strict harmonized regulations. Currently, collection from the natural environment and cultivation of this particular medicinal plant have occurred mainly in China, India, Kenya, Tanzania and Viet Nam.

The World Health Organization has recently developed a model monograph on good agricultural and collection practices (GACP) for *Artemisia annua* L based on the WHO guidelines on GACP for medicinal plants.

Reference: The WHO model monograph for GACP for *Artemisa annua* L. and the consultation report are available on http://www.who.int/medicines

Ayurvedic medicines and heavy metals

Canada — Health Canada is warning consumers not to use certain Ayurvedic medicinal products because they contain high levels of heavy metals such as lead, mercury and/or arsenic. Health Canada is taking action to remove these products from the market and to prevent further importation into Canada.

Ayurvedic medicinal products are used in traditional Indian healing and are often imported from India. According to the principles of Ayurvedic medicine, heavy metals may be used because of their reputed therapeutic properties. However, improper manufacturing processes may result in dangerously high levels of heavy metals remaining in the final product.

Heavy metals pose a particular health risk because they may accumulate in vital organs. Children are most susceptible to the toxic effects of heavy metal poisoning. For example, arsenic poisoning can cause nausea, abdominal pain, vomiting, muscle cramps, heart abnormalities, liver damage, anaemia and reduced motor nerve function. Lead poisoning can cause weight loss, insomnia, dizziness, swelling of the brain and paralysis. Mercury poisoning can cause tremors, insomnia, memory loss, slowed sensory and motor nerve function, and reduced mental function.

The following is a list of the unapproved Ayurvedic medicinal products found on the Canadian market thus far, which have been analysed and found to contain high levels of lead, mercury and/or arsenic:

- Karela tablets, produced by Shriji Herbal Products, India
- Karela capsules, produced by Himalaya Drug Co, India
- Karela capsules, produced by Charantia, UK (specifically batch #12011)
- Maha Sudarshan Churna powder, produced by Zandu Pharmaceuticals, Mumbai, India
- Maha Sudarshan Churna powder, D & K Pharmacy, Bhavnagar, India
- Maha Sudarshan Churna powder, produced by Chhatrisha, Lalpur, India
- Maha Sudarshan Churna powder, produced by Dabur India Ltd, New Delhi, India

- SAFI liquid, produced by Hamdard-WAKF-Pakistan
- SAFI liquid, produced by Hamdard-WAKF-India
- Yograj Guggul tablets, produced by Zandu Pharmaceuticals, Mumbai, India
- Sudarshan tablets, produced by Zandu Pharmaceuticals, Mumbai, India
- Shilajit capsules, produced by Dabur India Ltd, New Delhi, India

As a precaution, Health Canada advises Canadians not to use any other Karela, Safi, Maha Sudarshan Churna, Yograj Guggul, Sudarshan or Shilajit products unless they have the required market authorization.

Reference: Press release 2005-80, Health Canada warns consumers not to use certain Ayurvedic medicinal products. 14 July 2005.

National policy on regulation of herbal medicines

World Health Organization — Herbal medicines have always played an important role in human health. There are great differences among countries in the definition and categorization of herbal medicines: a single medicinal plant may be defined as a food, a functional food, a dietary supplement or a herbal medicine depending on the regulations applicable in each country. This makes it difficult for national drug regulation.

Requirements and methods for research and evaluation of the safety and efficacy of herbal medicines are more complex than for conventional pharmaceuticals. A single medicinal plant may contain hundreds of natural constituents and an analysis would be impossible in practice in the case of mixed herbal medicines.

The general lack of knowledge about herbal medicines and appropriate evaluation methods are factors that delay the creation or updating of national policies, laws and regulations. In order to meet these challenges WHO has conducted a global survey on national policies and regulation of herbal medicines. The results are stored in a global data base. Information is listed under 21 structural indicators intended to assess the policy and regulatory situation.

A report of the survey has been published. Sixty-one per cent of countries now have a registration system for herbal medicines, showing that progress has been made over recent years. The report contains a great deal of information, including regulatory status, requirements, number of products, and quality control measures existing in each country. The survey also identifies difficulties, including lack of research data, appropriate control mechanisms and lack of training.

Reference: World Health Organization. *National policy on traditional medicines and regulation of herbal medicines. report of a global survey.* Geneva, May 2005.

Regulatory guidelines for complementary medicines

Australia — In May 2003, the Australian Government established the Expert Committee on Complementary Medicines to review regulatory, health system and industry structures. The committee made 49 recommendations on a range of issues, including that a communication strategy be developed to better inform consumers of the potential risks associated with the personal importation of complementary medicines that may not be manufactured to the same standards of medicines available in Australia.

Australian Regulatory Guidelines for Complementary Medicines (ARGCM) have now been published with the aim to:

- provide information to help sponsors of complementary medicines to meet their obligations under therapeutic goods legislation;
- help ensure that applications to the TGA relating to complementary medicines uniformly meet all essential regulatory requirements so that applications may be processed successfully within minimum timeframes; and
- enhance clarity and transparency of processes leading to the Registration and Listing of complementary medicines in the Australian Register of Therapeutic Goods (ARTG).

Reference: http://www.tga.au/

Regulatory Action and News

Hydromorphone extended release suspended

United States of America — On request of the Food and Drug Administration (FDA), the sponsor of hydromorphone hydrochloride (Palladone®) extended release capsules, a potent narcotic painkiller, has agreed to suspend sales and marketing because of the potential for severe side effects if taken with alcohol.

Data has been provided to show that alcohol can cause high hydromorphone levels in the body, with potentially fatal effects. High drug levels of hydromorphone may depress or stop breathing, cause coma, and even death. Patients should contact their physician to discuss appropriate alternative treatments, including immediate release hydromorphone.

Palladone® is a time-release formulation of hydromorphone, a potent narcotic painkiller taken once-a-day with the capsule slowly releasing a steady amount of hydromorphone into the body. Hydromorphone is approved for treatment of moderate to severe chronic pain in opiate-tolerant patients and has been sold in the USA only since January 2005. To date, FDA is not aware of any patients who have had life-threatening side effects from drinking alcohol while taking hydromorphone.

Reference: *FDA Public Health Advisory* 13 July 2005. http://www.fda.gov/cder

New drug safety initiative

United States of America — The Food and Drug Administration (FDA) is launching a new programme to make drug safety information publicly available in an easily accessible format. Patients are taking a more active role in their healthcare, the FDA wants to make safety information available about the medicines they are using. The Drug Safety Initiative has the following components:

- Drug safety information located together in a new web location.
- Drug specific information for healthcare professionals, patients and other consumers.
- Draft Guidance: FDA's "Drug Watch" for Emerging Drug Safety Information.
- Federal Register Notice of Availability — Draft Guidance for Industry on the Food and Drug Administration's "Drug Watch'' for Emerging Drug Safety Information.
- Manual of Policies and Procedures (MaPP).
- Drug Safety Oversight Board Meetings.

Reference: Drug information on http://www.fda.gov/cder. 23 June 2005

Deregistration of thioridazine

Singapore — Thioridazine, a phenothiazine antipsychotic agent, is known to be associated with an increased risk of QT prolongation, cardiac arrhythmias and sudden death. Following emerging evidence of these safety concerns since 2000, the Health Sciences Agency (HSA) has strengthened the package inserts of all registered brands of thioridazine to warn of adverse effects.

Early this year, the manufacturer of the proprietary brand of thioridazine, Melleril®, announced worldwide voluntary withdrawal by 30 June 2005 because the risk-benefit balance no longer met current clinical and regulatory expectations. Although Melleril® is not marketed in Singapore, there are 4 generic brands currently registered: Aldazine®, Apo-thioridazine®, Merpazine® and Melibon®.

HSA sought the advice of its Pharmacovigilance Advisory Committee (PVAC) and local experts in the field of psychiatry on the balance of risks and benefits of thioridazine. Based on the evidence available, the PVAC arrived at an unfavourable risk-benefit outcome for the drug in view of the possibility of serious cardiac arrhythmias and the availability of alternative antipsychotic treatments. Hence, HSA will deregister the generic brands of thioridazine with effect 31 March 2006.

Reference: Product Safety Alert, 31 March 2005. http://www.hsa.gov.sg/cda/safetyalerts

Caution on self medication

Singapore — The Health Sciences Authority (HSA) has advised the public not to purchase any medicinal product from dubious sources such as street peddlers, unlicensed premises or via the Internet, as the safety, efficacy and quality of such products cannot be assured. Consumers are reminded to be cautious and sceptical about exaggerated health benefits and unrealistic personal testimonials accompanying medicinal and health products that sound too good to be true and to seek professional medical advice when self-medicating.

This advice by HSA arises from recent reports of adverse drug reactions submitted by healthcare professionals suspected to be associated with the use of some traditional medicines. They included blood disorders and liver injuries such as hepatitis and jaundice. Analytical testing confirmed that a number of these products were adulterated with very potent western drugs. Investigations revealed that the products in question were purchased overseas and brought into Singapore by consumers for their own use. The table below shows products found to be adulterated with one or more western medicines and potent drugs controlled as prescription-only medicines.

Reference: Press release, 17 June 2005. http://www.hsa.gov.sg.

European marketing authorizations

European Union — The Committee for Medicinal Products for Human Use (CHMP) gave positive opinions on initial marketing authorization applications for the following products.

- Aptivus® (**tipranavir**), from Boehringer Ingelheim International GmbH, for the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated adult patients with virus that is resistant to multiple protease inhibitors.

- Kepivance® (**palifermin**), from Amgen Europe B.V., for the prevention and treatment of oral mucositis in patients with haematological (blood and blood-forming tissues) cancers undergoing myoablative therapy, which suppresses bone marrow activity.

- Noxafil® (**posaconazole**) and Posaconazole SP® (posaconazole), from SP Europe, for the treatment of certain invasive fungal infections in patients whose disease did not respond to certain commonly used antifungal agents or who were intolerant of these other agents.

- Procoralan®/Corlentor® (**ivabradine**), from Les Laboratoires Servier, for the treatment of chronic stable angina pectoris.

- Revatio® (**sildenafil** citrate), from Pfizer Limited, for the treatment of pulmonary arterial hypertension.

Table: Examples of adulterated products

Product name	Use	Adulterant(s)
Jamu Kenis Pil, Borobudur, Semarang, Indonesia	For symptoms such as frequent feeling of thirst, good appetite but continued weight loss, weakness, slow recovery when ill, tiredness, blurred vision and frequent urination.	Per pill: glibenclamide 0.03 mg.
Jamu Pegal Linu, PJ. Guna Sehat, Suryo Sudarmo, Cilacap, Indonesia	Body ache, rheumatism, blurred vision, disability, stroke and lethargy.	Per packet: dipyrone 25.7 mg phenylbutazone 6.1 mg.
Kapsul Asam Urat (TCU), Prananda Jaya Sukses, Indonesia	Nerve ache, waist pain, rheumatism, stiff muscle, leg swelling, listlessness & insomnia.	Per capsule: phenylbutazone 89.73 mg paracetamol 173.32 mg

• ® Xolair (**omalizumab**), from Novartis Europharm Ltd., for the treatment of severe persistent allergic asthma.

Extension of indications and other recommendations

The Committee for Medicinal Products for Human Use (CHMP) adopted opinions for the extension of indications of products that are already authorized on the European Union.

• Keppra® (**levetiracetam**), UCB S.A., to extend the indication of adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization to children from 4 years of age with epilepsy. Keppra was first authorized in the European Union on 29 September 2000.

• Remicade® (**infliximab**), Centocor B.V., to extend its indication to include treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systematic therapy including cyclosporine, methotrexate or PUVA.

• The Committee recommended a new contraindication for Forsteo® (**teriparatide**) to exclude patients with skeletal malignancies or bone metastases from treatment.

Summaries of opinion for initial marketing authorization applications, extensions of indication and other recommendations are available on http://www.emea.eu.int

Reference: *EMEA Press Release*, 28 July 2005. European Medicines Agency, Committee for Medicinal Products for Human Use, 25–28 July 2005 Doc. Ref: EMEA/246640/2005

Tigecycline: first-in-class antibiotic approved

United States of America — The Food and Drug Administration (FDA) has approved tigecycline (Tygacil®), a novel I.V. antibiotic with a broad spectrum of antimicrobial activity, including activity against methicillin-resistant *Staphylococcus aureus* (MRSA) which provides a treatment alternative for complicated skin and intra-abdominal Infections in adults. Approval of this first-in-class product comes at a time when the need for new antibiotic options to combat serious, resistant infections is increasing. Tigecycline is the first antibiotic approved in a new class called glycylcyclines, developed to overcome key mechanisms of resistance that have affected antibiotic use.

The FDA was provided with data from four pivotal phase III studies examining the safety and efficacy of tigecycline for the treatment of cIAI and cSSSI. The submission also included in vitro data showing activity against both Gram-negative and Gram-positive bacteria, anaerobes, and certain drug-resistant pathogens. The manufacturer now awaits decisions on approval of tigecycline from other regulatory bodies including those in the European Union, Australia, Brazil, Canada, Colombia, Mexico, South Africa, Switzerland, Taiwan, and Venezuela.

Tigecycline is contraindicated in patients with known hypersensitivity and administered with caution in patients with known hypersensitivity to tetracycline class antibiotics. In clinical trials, the most common treatment-emergent adverse events were nausea (29.5 percent) and vomiting (19.7 percent).

Tigecycline may cause fetal harm when administered to a pregnant woman. Safety and effectiveness in patients below age 18 and lactating women have not been established. Use of tigecycline during tooth development may cause permanent discoloration of the teeth. Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range from mild to life threatening. Monotherapy should be used with caution in patients with clinically apparent intestinal perforation.

Reference: Communication from Wyeth 15 June 2005 at http://www.wyeth.com

Essential Medicines

Highlights of the 14th Model List of Essential Medicines

The WHO Expert Committee on the Selection and Use of Essential Medicines met in Geneva in March 2005. Their task was to evaluate evidence-based material relating to the maintenance and updating of the Model List of Essential Medicines. The Model List presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost effective medicines for priority conditions. Two important items from the draft report (http://www.who.int/medicines/library/general/1-ReportFinal-unedited_010705.pdf) are presented below and the latest revision of the 14th Model List of Essential Medicines can be found on page 224.

Methadone and buprenorphine

Most illicit opioid use is heroin use and it is estimated that there are 12.6 million injecting drug users (IDUs) worldwide. Around 10% of HIV infections are associated with injecting drug use and users are also exposed to a high risk of hepatitis B and C. Treatment of heroin dependence is therefore of high public health relevance.

Both buprenorphine and methadone are effective for the treatment of heroin dependence (1, 2). However, methadone maintenance therapy at appropriate doses is the most effective in retaining patients in treatment and suppressing heroin use (3). Methadone is less costly than buprenorphine. It was reported that the cost of buprenorphine per patient per year varied from US$ 300–600 for the generic product to approximately US$ 1750–3500 as a branded product. Besides conventional randomized controlled trials with abstinence rate as an outcome, there is evidence of effectiveness in various societal effects (such as a reduction in criminality) which should also be taken into consideration.

The Expert Committee noted that the use of methadone reduces seroconversion of HIV/AIDS and interacts with antiretroviral medicines, but that this only affects the serum level of methadone, requiring adjustment to the patient response. The Committee therefore recommended that methadone (and buprenorphine, as being within the same pharmacological class) be added to the complementary list, within a new subsection 24.5 “Medicines used in substance dependence programmes” and a note that these products should only be used within an established support programme.

References

1. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or metha-done maintenance for opioid dependence. *The Cochrane Database of Systematic Reviews* 2003, Issue 2. http://www.cochrane.org/cochrane/revabstr/AB002207.htm,

2. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *The Cochrane Database of Systematic Reviews* 2003, Issue 2. http://www.cochrane.org/cochrane/revabstr/AB002209.htm.

3. Amato L, Davoli M, Ferri M, Perucci C, Effectiveness of opiate maintenance therapies: an overview of systematic reviews. Cochrane Colloquia, Ottawa 2004 http://www.cochrane.org/colloquia/ abstracts/ottawa/P-004.htm.

Mifepristone with misoprostol

A review of 39 trials (1) indicated that administration of mifepristone followed by misoprostol within 36 to 48 hours is effective in inducing medical abortion of up to 9-weeks of pregnancy. Major complications seem to be rare, the most common complication being blood transfusion (about 0.2%). It was reported that the side-effects were mainly due to prostaglandins and involved nausea, vomiting, and diarrhoea. In comparison to surgical abortion, (2) the risks of bleeding, abdominal pain, fever and dizziness in the medical abortion population were higher than those in the surgical abortion population. In addition, the duration of bleeding caused by medical abortion was longer than that caused by surgical abortion.

Mifepristone followed by misoprostol for medical abortion in the first nine weeks of pregnancy has been registered in the following countries in Europe: Austria, Belgium, Finland, France,

Germany, Greece, Luxembourg, the Netherlands, Norway, Romania, Spain, Sweden, Switzerland and the UK. The regimen has also been registered in Azerbaijan, Georgia, India, Israel, New Zealand, the People's Republic of China, the Russian Federation, South Africa, Tunisia, Ukraine, the USA, Uzbekistan and Viet Nam.

The Committee recommended that mifepristone and misoprostol be included on the complementary list of the Model List section 22 for medical abortion within nine weeks of pregnancy, and that the following footnote be added: "Requires close medical supervision". In reviewing the recommendation relating to this combination of products, the Director-General of WHO has added a note adjacent to the combination in the Model List stating "Where permitted under national law and where culturally acceptable".

References

1. Kulier R, G|lmezoglu AM, Hofmeyr GJ, Cheng LN, Campana A. Medical methods for first trimester abortion. The Cochrane Database of Systematic Reviews 2004, Issue 2 (http://www.cochrane.org/cochrane/revabstr/AB002855.htm)

2. Zou Y, Li YP, Lei ZW, Lu L, Jiang S, Li Q. Side effect of mifepristone in combination with misoprostol for medical abortion. *Zhonghua Fu Chan Ke Za Zhi* 2004; **39**: 39-42.

3. 14th Expert Committee on the Selection and Use of Essential Medicines Geneva, 7-11 March 2005, unedited report of the Committee is at: http://www.who.int/medicines/library/general/1-ReportFinal-unedited_010705.pdf

4. WHO Model List of Essential Medicines, in Arabic, Chinese, English, French, Spanish and Russian. Available at: http://www.who.int/medicines/organization/par/edl/eml/shtml

Additions and deletions to the WHO Model List of Essential Medicines 2005

Deletions

1.1	ether
2.3	colchicine
5	clonazepam
6.2.2	nalidixic acid
6.2.5	thioacetazone + isoniazid
6.6	diethyltoluamide
7.1	ergotamine
11.1	polygeline
12.2	isoprenaline
13.7	sun protection agents
17.3	local anaesthetics, astringent, antiinflammatory as anti-haemorrhoidal
17.4	atropine as spasmolytic
21.1	silver nitrate eye solution
22.1	ergometrine tablet
22.2.2	salbutamol as tocolytic
25	theophylline, aminophylline, cromoglicic acid.

Additions

6.2.1	cefixime tablet 400 mg
6.3	clotrimazole 1%, 10% vaginal cream; 100, 500 mg vaginal tablets
17.5.2	zinc sulfate tablet or syrup in 10 mg per unit dosage
22.1	misoprostol 25 microgram intravaginal tablet; mifepristone 200 mg oral tablet – misoprostol 200 microgram tablet
22.2	nifedipine 10 mg capsule as tocolytic
24.5	methadone oral solution 5mg/5ml, 10 mg/5ml, or concentrate for oral solution 5mg/ml, 10 mg/ml

WHO Model List of Essential Medicines

Core List (revised March 2005)

1: Anaesthetics

1.1 General anaesthetics and oxygen

■ halothane	inhalation
ketamine	injection, 50 mg (as hydrochloride)/ml in 10-ml vial
nitrous oxide	inhalation
oxygen	inhalation (medicinal gas)
■ thiopental	powder for injection, 0.5 g, 1.0 g (sodium salt) in ampoule

1.2 Local anaesthetics

■ bupivacaine	injection, 0.25%, 0.5% (hydrochloride) in vial injection for spinal anaesthesia, 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 7.5% glucose solution
■ lidocaine	injection, 1%, 2% (hydrochloride) in vial injection for spinal anaesthesia, 5% (hydrochloride) in 2-ml ampoule to be mixed with 7.5% glucose solution topical forms, 2-4% (hydrochloride)
lidocaine + epinephrine (adrenaline)	injection 1%, 2% (hydrochloride)+ epinephrine 1:200 000 in vial; dental cartridge 2% (hydrochloride) + epinephrine 1:80 000

Complementary List

ephedrine	injection, 30 mg (hydrochloride)/ml in 1-ml ampoule (For use in spinal anaesthesia during delivery, to prevent hypotension)

1.3 Preoperative medication and sedation for short-term procedures

atropine	injection, 1 mg (sulfate) in 1-ml ampoule
■ diazepam	injection, 5 mg/ml in 2-ml ampoule; tablet, 5 mg

Explanatory Notes

The **core list** presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

When the strength of a drug is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word “as”.

The square box symbol (■) is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

Drugs are listed in alphabetical order, within sections.

morphine	injection, 10 mg (sulfate or hydrochloride) in 1-ml ampoule
promethazine	elixir or syrup, 5 mg (hydrochloride)/5ml

2. Analgesics, antipyretics, non-steroidal anti-inflammatory medicines (NSAIMs), medicines to treat gout and disease modifying agents in rheumatoid disorders (DMARDs)

2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)

acetylsalicylic acid	tablet, 100-500 mg; suppository, 50-150 mg
ibuprofen	tablet, 200 mg, 400 mg
paracetamol*	tablet, 100-500 mg; suppository, 100 mg; syrup, 125 mg/5ml

** not recommended for anti-inflammatory use due to lack of proven benefit to that effect.*

2.2 Opioid analgesics

codeine	tablet, 30 mg (phosphate)
morphine	injection, 10 mg in 1-ml ampoule (sulfate or hydrochloride); oral solution, 10 mg (hydrochloride or sulfate)/5 ml; tablet, 10 mg (sulfate)

2.3 Medicines used to treat gout

allopurinol	tablet, 100 mg

2.4 Disease modifying agents used in rheumatoid disorders (DMARDs)

chloroquine	tablet, 100 mg, 150 mg (as phosphate or sulfate)
Complementary List	
azathioprine	*tablet, 50 mg*
methotrexate	*tablet, 2.5 mg (as sodium salt)*
penicillamine	*capsule or tablet, 250 mg*
sulfasalazine	*tablet, 500 mg*

3. Antiallergics and medicines used in anaphylaxis

■ chlorphenamine	tablet, 4 mg (hydrogen maleate); injection, 10 mg (hydrogen maleate) in 1-ml ampoule
dexamethasone	injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule
epinephrine (adrenaline)	injection, 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule
hydrocortisone	powder for injection, 100 mg (as sodium succinate) in vial
■ prednisolone*	tablet, 5 mg, 25 mg

** there is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses.*

4. Antidotes and other substances used in poisonings

Section 4 will be reviewed at the next meeting of the Expert Committee on the Selection and Use of Essential Medicines.

4.1 Non-specific

charcoal, activated	powder

4.2 Specific

acetylcysteine	injection, 200 mg/ml in 10-ml ampoule
atropine	injection, 1 mg (sulfate) in 1-ml ampoule
calcium gluconate	injection, 100 mg/ml in 10-ml ampoule
deferoxamine	powder for injection, 500 mg (mesilate) in vial
dimercaprol	injection in oil, 50 mg/ml in 2-ml ampoule
DL-methionine	tablet, 250 mg
methylthioninium chloride (methylene blue)	injection, 10 mg/ml in 10-ml ampoule
naloxone	injection, 400 micrograms (hydrochloride) in 1-ml ampoule
penicillamine	capsule or tablet, 250 mg
potassium ferric hexacyanoferrate(II)-$2H_20$ (Prussian blue)	powder for oral administration
sodium calcium edetate	injection, 200 mg/ml in 5-ml ampoule
sodium nitrite	injection, 30 mg/ml in 10-ml ampoule
sodium thiosulfate	injection, 250 mg/ml in 50-ml ampoule

5. Anticonvulsants/anti-epileptics

carbamazepine — scored tablet, 100 mg, 200 mg
■ diazepam — injection, 5 mg/ml in 2-ml ampoule (intravenous or rectal)

magnesium sulfate* — injection, 500 mg/ml in 2-ml ampoule; 500mg/ml in 10-ml ampoule

** for use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.*

phenobarbital — tablet, 15-100 mg; elixir, 15 mg/5ml

phenytoin — capsule or tablet, 25 mg, 50 mg, 100 mg (sodium salt); injection, 50 mg/ml in 5-ml vial (sodium salt)

valproic acid — enteric coated tablet, 200 mg, 500 mg (sodium salt)

Complementary List

ethosuximide — *capsule, 250 mg; syrup, 250 mg/5ml*

6. Anti-infective medicines

6.1 Anthelminthics

6.1.1 Intestinal anthelminthics

albendazole — chewable tablet, 400 mg

levamisole — tablet, 50 mg; 150 mg (as hydrochloride)

■ mebendazole — chewable tablet, 100 mg, 500 mg

niclosamide* — chewable tablet, 500 mg

** niclosamide is listed for use when praziquantel treatment fails*

praziquantel — tablet, 150 mg, 600 mg

pyrantel — chewable tablet 250 mg (as embonate); oral suspension, 50 mg (as embonate)/ml

6.1.2 Antifilarials

ivermectin — scored tablet, 3 mg, 6 mg

Complementary List

diethylcarbamazine — *tablet, 50 mg, 100 mg (dihydrogen citrate)*

suramin sodium — *powder for injection, 1 g in vial*

6.1.3 Antischistosomals and antitrematode medicine

praziquantel — tablet, 600 mg

triclabendazole — tablet, 250 mg

Complementary List

*oxamniquine** — *capsule, 250 mg; syrup, 250 mg/5ml*

** oxamniquine is listed for use when praziquantel treatment fails.*

6.2 Antibacterials

6.2.1 Beta Lactam medicines

Applications for cefalexin and cefazolin are anticipated for the next meeting of the Expert Committee.

amoxicillin — capsule or tablet, 250 mg, 500 mg (anhydrous); powder for oral suspension, 125 mg (anhydrous)/5 ml

amoxicillin + clavulanic acid — tablet, 500 mg + 125 mg

ampicillin — powder for injection, 500 mg, 1 g (as sodium salt) in vial

benzathine benzylpenicillin — powder for injection, 1.44 g benzylpenicillin (=2.4 million IU) in 5-ml vial

benzylpenicillin — powder for injection, 600 mg (= 1 million IU), 3 g (= 5 million IU) (sodium or potassium salt) in vial

cefixime* — capsule 400mg

** only listed for single dose treatment of uncomplicated ano-genital gonorrhoea*

■ cloxacillin
capsule, — 500 mg, 1 g (as sodium salt); powder for oral solution, 125 mg (as sodium salt)/5 ml; powder for injection, 500 mg (as sodium salt) in vial

phenoxymethylpenicillin — tablet, 250 mg (as potassium salt); powder for oral suspension, 250 mg (as potassium salt)/5 ml

procaine benzylpenicillin — powder for injection, 1 g (=1 million IU), 3 g (=3 million IU) in vial

Complementary List

ceftazidime — *powder for injection, 250 mg (as pentahydrate) in vial*

■ *ceftriaxone* — *powder for injection, 250 mg, 1 g (as sodium salt) in vial*

imipenem + cilastatin**	*powder for injection 250 mg (as monohydrate) + 250 mg (as sodium salt), 500 mg (as monohydrate) + 500 mg (as sodium salt) in vial*

** only listed for the treatment of life-threatening hospital-based infection due to suspected or proven multidrug resistant infection.*

6.2.2 Other antibacterials

azithromycin*	capsule, 250 mg or 500 mg; suspension 200 mg/5 ml

** only listed for single dose treatment of genital C. trachomatis and of trachoma*

chloramphenicol	capsule, 250 mg; oral suspension, 150 mg (as palmitate)/5 ml; powder for injection, 1 g (sodium succinate) in vial; oily suspension for injection 0.5 g (as sodium succinate)/ml in 2-ml ampoule
■ ciprofloxacin*	tablet 250 mg (as hydrochloride)

** final selection depends on indication for use.*

doxycycline*	capsule or tablet, 100 mg (hydrochloride)

** final selection depends on indication for use.*

■ erythromycin	capsule or tablet, 250 mg (as stearate or ethyl succinate); powder for oral suspension, 125 mg (as stearate or ethyl succinate); powder for injection, 500 mg (as lactobionate) in vial
■ gentamicin*	injection, 10 mg, 40 mg (as sulfate)/ml in 2-ml vial

** final selection depends on indication for use.*

■ metronidazole	tablet, 200-500 mg; injection, 500 mg in 100-ml vial; suppository, 500 mg, 1 g; oral suspension, 200 mg (as benzoate)/5 ml
nitrofurantoin	tablet, 100 mg
spectinomycin	powder for injection, 2 g (as hydrochloride) in vial
sulfamethoxazole + trimethoprim	tablet, 100 mg + 20 mg, 400 mg + 80 mg; oral suspension, 200 mg + 40 mg/5 ml; injection, 80 mg + 16 mg/ml in 5-ml and 10-ml ampoules
trimethoprim	tablet, 100 mg, 200 mg

Complementary List

clindamycin	*capsule, 150 mg; injection, 150 mg (as phosphate)/ml*
sulfadiazine	*tablet, 500 mg; injection, 250 mg (sodium salt) in 4-ml ampoule*
vancomycin	*powder for injection, 250 mg (as hydrochloride) in vial*

6.2.3 Antileprosy medicines

Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (Multi Drug Therapy blister packs) containing standard two medicine (paucibacillary leprosy) or three medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

clofazimine	capsule, 50 mg, 100 mg
dapsone	tablet, 25 mg, 50 mg, 100 mg
rifampicin	capsule or tablet, 150 mg, 300 mg

6.2.4 Antituberculosis medicines

ethambutol	tablet, 100 mg-400 mg (hydrochloride)
isoniazid	tablet, 100-300 mg
isoniazid + ethambutol	tablet, 150 mg + 400 mg
pyrazinamide	tablet, 400 mg
rifampicin	capsule or tablet, 150 mg, 300 mg
rifampicin + isoniazid	tablet, 60 mg + 30 mg; 150 mg + 75 mg; 300 mg + 150 mg; 60 mg + 60 mg *(For intermittent use three times weekly);* 150 mg + 150 mg *(For intermittent use three times weekly)*
rifampicin + isoniazid + pyrazinamide	tablet, 60 mg + 30 mg + 150 mg; 150 mg + 75 mg + 400 mg 150 mg + 150 mg + 500 mg *(For intermittent use three times weekly)*
rifampicin + isoniazid + pyrazinamide + ethambutol	tablet, 150 mg + 75 mg + 400 mg + 275 mg
streptomycin	powder for injection, 1 g (as sulfate) in vial

Complementary List

Reserve second-line drugs for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards

for TB control. These medicines will be reviewed at the next meeting of the Expert Committee.

amikacin	*powder for injection, 1000 mg in vial*
p-aminosalicylic acid	*tablet, 500 mg; granules, 4 g in sachet*
capreomycin	*powder for injection, 1000 mg in vial*
ciprofloxacin	*tablet, 250 mg, 500 mg*
cycloserine	*capsule or tablet, 250 mg*
ethionamide	*tablet, 125 mg, 250 mg*
kanamycin	*powder for injection, 1000 mg in vial*
levofloxacin	*tablet, 250 mg, 500 mg*
ofloxacin	*tablet, 200 mg, 400 mg*

6.3 Antifungal medicines

clotrimazole	vaginal tablet, 100 mg, 500 mg, vaginal cream 1%, 10%
■ fluconazole	capsule 50 mg; injection 2 mg/ml in vial; oral suspension 50 mg/5-ml
griseofulvin	capsule or tablet, 125 mg, 250 mg
nystatin	tablet, 100 000, 500 000 IU; lozenge 100 000 IU; pessary, 100 000 IU

Complementary List

amphotericin B	*powder for injection, 50 mg in vial*
flucytosine	*capsule, 250 mg; infusion, 2.5 g in 250 ml*
potassium iodide	*saturated solution*

6.4 Antiviral medicines

6.4.1 Antiherpes medicines

■ aciclovir	tablet, 200 mg; powder for injection 250 mg (as sodium salt) in vial

6.4.2 Antiretrovirals

Adequate resources and specialist oversight are prerequisites for the introduction of this class of drugs. The antiretroviral drugs do not cure HIV infection, they only temporarily suppress viral replication and improve symptoms. They have various adverse effects and patients receiving these drugs require careful monitoring by adequately trained health professionals. For these reasons, continued rigorous promotion of measures to prevent new infections is essential and the need for this has not been diminished in any way by the addition of antiretroviral drugs to the Model List. Adequate resources and trained health professionals are a prerequisite for the introduction of this class of drugs. Effective therapy requires commencement of three or four drugs simultaneously, and alternative regimens are necessary to meet specific requirements at start-up, to substitute for first-line regimens in the case of toxicity, or to replace failing regimens. In order to simplify treatment, facilitate storage and distribution, and improve patient adherence to the treatment plan, the Committee recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations. These include modified dosage forms, non-refrigerated formulations and paediatric formulations with assured pharmaceutical quality and interchangeability with the single products as approved by the relevant drug regulatory authority.

6.4.2.1 Nucleoside reverse transcriptase inhibitors

abacavir (ABC)	tablet, 300 mg (as sulphate), oral solution, 100 mg (as sulphate)/5ml
didanosine (ddI)	buffered chewable, dispersible tablet, 25mg, 50mg, 100mg, 150mg, 200mg buffered powder for oral solution, 100 mg, 167 mg, 250 mg packets unbuffered enteric coated capsule, 125 mg, 200 mg, 250 mg, 400 mg
lamivudine (3TC)	tablet, 150mg, oral solution 50 mg/5ml
stavudine (d4T)	capsule 15mg, 20 mg, 30 mg, 40 mg, powder for oral solution, 5 mg/5ml
zidovudine (ZDV or AZT)	tablet, 300 mg capsule 100 mg, 250 mg oral solution or syrup, 50 mg/5ml solution for IV infusion injection, 10 mg/ml in 20-ml vial

6.4.2.2 Non-nucleoside reverse transcriptase inhibitors

efavirenz (EFV or EFZ)	capsule, 50 mg, 100 mg, 200 mg oral solution, 150 mg/5ml
nevirapine (NVP)	tablet 200 mg; oral suspension 50 mg/5-ml

6.4.2.3 Protease inhibitors

Selection of two or three protease inhibitors from the Model List will need to be determined by each country after consideration of local treatment guidelines and experience, as well as the comparative costs of available products. Ritonavir is recommended for use in combination with indinavir, lopinavir and saquinavir as a booster, and not as a drug in its own right.

indinavir (IDV)	capsule, 200 mg, 333 mg, 400 mg (as sulfate)
ritonavir	capsule, 100 mg, oral solution 400 mg/5ml
lopinavir + ritonavir (LPV/r)	capsule, 133.3 mg + 33.3 mg, oral solution, 400 mg + 100 mg/5ml
nelfinavir (NFV)	tablet, 250 mg (as mesilate), oral powder 50 mg/g
saquinavir (SQV)	capsule, 200 mg

6.5 Antiprotozoal medicines

6.5.1 Antiamoebic and antigiardiasis medicines

diloxanide	tablet, 500 mg (furoate)
■ metronidazole	tablet, 200-500 mg; injection, 500 mg in 100-ml vial; oral suspension 200 mg (as benzoate)/5 ml

6.5.2 Antileishmaniasis medicines

■ meglumine antimoniate	injection, 30%, equivalent to approximately 8.1% antimony in 5-ml ampoule

Complementary List

amphotericin B	*powder for injection, 50 mg in vial*
pentamidine	*powder for injection, 200 mg, 300 mg (isetionate) in vial*

6.5.3 Antimalarial medicines

6.5.3.1 For curative treatment

Medicines for the treatment of *P. falciparum* malaria cases should be used in combination.

amodiaquine*	tablet, 153 mg or 200 mg (base)

** amodiaquine should preferably be used as part of combination therapy.*

artemether + lumefantrine*	tablet, 20 mg + 120 mg

** recommended for use in areas with significant drug resistance and not in pregnancy or in children below 10 kg*

chloroquine	tablet 100 mg, 150 mg (as phosphate or sulfate); syrup, 50 mg (as phosphate or sulfate)/5 ml; injection 40 mg (as hydrochloride, phosphate or sulfate)/ml in 5-ml ampoule
primaquine	tablet, 7.5 mg, 15 mg (as diphosphate)
quinine	tablet, 300 mg (as bisulfate or sulfate); injection, 300 mg (as dihydrochloride)/ml in 2-ml ampoule

Complementary List

artemether	*injection, 80 mg/ml in 1-ml ampoule*
artesunate	*tablet, 50 mg*
doxycycline	*capsule or tablet, 100 mg (hydrochloride) (for use only in combination with quinine)*
mefloquine	*tablet, 250 mg (as hydrochloride)*
sulfadoxine + pyrimethamine	*tablet, 500 mg + 25 mg*

6.5.3.2 For prophylaxis

chloroquine	tablet, 150 mg (as phosphate or sulfate); syrup, 50 mg (as phosphate or sulfate)/5 ml
doxycycline	capsule or tablet, 100 mg (hydrochloride)
mefloquine	tablet, 250 mg (as hydrochloride)
proguanil	tablet, 100 mg (hydrochloride) *(for use only in combination with chloroquine)*

6.5.4 Anti-pneumocystosis and antitoxoplasmosis medicines

pyrimethamine	tablet, 25 mg
sulfamethoxazole + trimethoprim	injection 80 mg + 16 mg/ml in 5-ml ampoule 80 mg + 16 mg/ml in 10-ml ampoule

Complementary List

pentamidine	*tablet 200 mg, 300 mg*

6.5.5. Antitrypanosomal medicines

6.5.5.1 African trypanosomiasis

melarsoprol	injection, 3.6% solution
suramin sodium	powder for injection, 1 g in vial

Complementary List

eflornithine	*injection, 200 mg (hydrochloride)/ml in 100-ml bottles*
pentamidine	*powder for injection, 200 mg, 300 mg (isetionate) in vial*

6.5.5.2 American tripanosomiasis

benznidazole	tablet, 100 mg
nifurtimox	tablet, 30 mg; 120 mg; 250 mg

7. Antimigraine medicines

7.1 For treatment of acute attack

acetylsalicylic acid	tablet, 300-500 mg

paracetamol tablet, 300-500 mg

7.2 For prophylaxis

■ propranolol tablet, 20 mg, 40 mg (hydrochloride)

8. Antineoplastic, immunosuppressives and medicines used in palliative care

8.1 Immunosuppressive medicines

Complementary List

azathioprine *tablet, 50 mg; powder for injection, 100 mg (as sodium salt) in vial*

ciclosporin *capsule, 25 mg; concentrate for injection 50 mg/ml in 1-ml ampoule for organ transplantation*

8.2 Cytotoxic medicines

Complementary List

asparaginase *powder for injection, 10 000 IU in vial*

bleomycin *powder for injection, 15 mg (as sulfate) in vial*

calcium folinate *tablet, 15 mg; injection, 3 mg/ml in 10-ml ampoule*

chlorambucil *tablet 2 mg*

chlormethine *powder for injection, 10 mg (hydrochloride) in vial*

cisplatin *powder for injection, 10 mg, 50 mg in vial*

cyclophosphamide *tablet, 25 mg; powder for injection, 500 mg in vial*

cytarabine *powder for injection, 100 mg in vial*

dacarbazine *powder for injection, 100 mg in vial*

dactinomycin *powder for injection, 500 micrograms in vial*

daunorubicin *powder for injection, 50 mg (as hydrochloride)*

doxorubicin *powder for injection, 10 mg, 50 mg (hydrochloride) in vial*

etoposide *capsule, 100 mg; injection, 20 mg/ml in 5-ml ampoule*

fluorouracil *injection, 50 mg/ml in 5-ml ampoule*

levamisole *tablet, 50 mg (as hydrochloride)*

mercaptopurine *tablet, 50 mg*

methotrexate *tablet, 2.5 mg (as sodium salt); powder for injection, 50 mg (as sodium salt) in vial*

procarbazine *capsule, 50 mg (as hydrochloride)*

vinblastine *powder for injection, 10 mg (sulfate) in vial*

vincristine *powder for injection, 1 mg, 5 mg (sulfate) in vial*

8.3 Hormones and antihormones

Complementary List

dexamethasone *injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule*

hydrocortisone *powder for injection, 100 mg (as sodium succinate) in vial*

■ *prednisolone** *tablet, 5 mg, 25 mg*

** there is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses.*

tamoxifen tablet, 10 mg, 20 mg (as citrate)

8.4 Medicines used in palliative care

The WHO Expert Committee on the Selection and Use of Essential Medicines recommended that all the drugs mentioned in the WHO publication Cancer Pain Relief: with a Guide to Opioid Availability, second edition, be considered essential. The drugs are included in the relevant sections of the Model List, according to their therapeutic use, e.g. analgesics.

9. Antiparkinsonism medicines

biperiden tablet, 2 mg (hydrochloride); injection, 5 mg (lactate) in 1-ml ampoule

levodopa + carbidopa tablet, 100 mg + 10 mg; 250 mg + 25 mg

10. Medicines affecting the blood

10.1 Antianaemia medicines

ferrous salt tablet, equivalent to 60 mg iron; oral solution equivalent to 25 mg iron (as sulfate)/ml

ferrous salt + folic acid tablet equivalent to 60 mg iron + 400 micrograms folic acid (nutritional supplement for use during pregnancy.)

folic acid tablet 1 mg, 5 mg

hydroxocobalamin injection, 1 mg in 1-ml ampoule

10.2 Medicines affecting coagulation

heparin sodium — injection, 1000 IU/ml, 5000 IU/ml, 20,000 IU/ml in 1-ml ampoule

phytomenadione — injection, 10 mg/ml in 5-ml ampoule; tablet, 10 mg

protamine sulfate — injection, 10 mg/ml in 5-ml ampoule

■ warfarin — tablet, 1 mg, 2 mg and 5 mg (sodium salt)

11. Blood products and plasma substitutes

11.1 Plasma substitutes

■ dextran 70* — injectable solution, 6%

* polygeline, injectable solution, 3.5% is considered as equivalent

11.2 Plasma fractions for specific use

All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components, and Plasma Derivatives (Revised 1992). (WHO Technical Report Series, No. 840, 1994, Annex 2).

Complementary List

■ *factor VIII concentrate* — *dried*

■ *factor IX complex (coagulation factors, II, VII, IX, X) concentrate* — *dried*

12. Cardiovascular medicines

12.1 Antianginal medicines

■ atenolol — tablet, 50 mg, 100 mg

glyceryl trinitrate — tablet (sublingual), 500 micrograms

■ isosorbide dinitrate — tablet (sublingual), 5 mg

verapamil — tablet, 40 mg, 80 mg (hydrochloride)

12.2 Antiarrhythmic medicines

This subsection will be reviewed at the next meeting of the Expert Committee when it is anticipated that applications for amiodarone and sotalol will be received.

■ atenolol — tablet, 50 mg, 100 mg

digoxin — tablet, 62.5 micrograms, 250 micrograms; oral solution 50 micrograms/ml; injection 250 micrograms/ml in 2-ml ampoule

epinephrine (adrenaline) — injection, 1 mg (as hydrochloride)/ml in ampoule

lidocaine — injection, 20 mg (hydrochloride)/ml in 5-ml ampoule

verapamil — tablet, 40 mg, 80 mg (hydrochloride); injection, 2.5 mg (hydrochloride)/ml in 2-ml ampoule

Complementary List

■ *procainamide* — *injection, 100 mg (hydrochloride)/ml in 10-ml ampoule*

■ *quinidine* — *tablet, 200 mg (sulfate)*

12.3 Antihypertensive medicines

■ amlodipine — tablet, 5mg

■ atenolol — tablet, 50 mg, 100 mg

■ enalapril — tablet, 2.5 mg

hydralazine* — tablet, 25 mg, 50 mg (hydrochloride); powder for injection, 20 mg (hydrochloride) in ampoule

** hydralazine is listed for use in the acute management of severe pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines.*

■ hydrochlorothiazide — scored tablet, 25 mg

methyldopa* — tablet, 250 mg

** methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines.*

Complementary List

sodium nitroprusside — *powder for infusion, 50 mg in ampoule*

12.4 Medicines used in heart failure

This subsection will be reviewed at the next meeting of the Expert Committee.

digoxin — tablet, 62.5 micrograms, 250 micrograms; oral solution, 50 micrograms/ml; injection, 250 micrograms/ml in 2-ml ampoule

■ enalapril — tablet, 2.5 mg

■ furosemide — tablet, 40 mg; injection, 10 mg/ml in 2-ml ampoule

■ hydrochlorothiazide — scored tablet, 25 mg

Complementary List

dopamine	*injection, 40 mg (hydrochloride) in 5-ml vial*

12.5 Antithrombotic medicines

acetylsalicylic acid	tablet, 100 mg
Complementary List	*streptokinase powder for injection, 1.5 million IU in vial*

12.6 Lipid-lowering agents

The WHO Expert Committee on the Selection and Use of Essential Medicines recognizes the value of lipid-lowering drugs in treating patients with hyperlipidaemia. HMG-CoA reductase inhibitors, often referred to as "statins", are a family of potent and effective lipid-lowering drugs with a good tolerability profile. Several of these drugs have been shown to reduce the incidence of fatal and non-fatal myocardial infarction, stroke and mortality (all causes), as well as the need for coronary by-pass surgery. All remain very costly but may be cost effective for secondary prevention of cardiovascular disease as well as for primary prevention in some very high-risk patients. Since no single drug has been shown to be significantly more effective or less expensive than others in the group, none is included in the Model List; the choice of drug for use in patients at highest risk should be decided at the national level.

13. Dermatological medicines (topical)

13.1 Antifungal medicines

benzoic acid + salicylic acid	ointment or cream, 6% + 3%
■ miconazole	ointment or cream, 2% (nitrate)
sodium thiosulfate	solution, 15%
Complementary List	
selenium sulfide	*detergent-based suspension, 2%*

13.2 Anti-infective medicines

■ methylrosanilinium chloride (gentian violet)	aqueous solution, 0.5%; tincture, 0.5%
neomycin sulfate + bacitracin	ointment, 5 mg neomycin sulfate + 500 IU bacitracin zinc/g
potassium permanganate	aqueous solution 1:10 000
silver sulfadiazine	cream, 1%, in 500-g container

13.3 Anti-inflammatory and antipruritic medicines

■ betamethasone	ointment or cream, 0.1% (as valerate)
■ calamine lotion	lotion
■ hydrocortisone	ointment or cream, 1% (acetate)

13.4 Astringent medicines

aluminium diacetate	solution, 13% for dilution

13.5 Medicines affecting skin differentiation and proliferation

benzoyl peroxide	lotion or cream, 5%
coal tar	solution, 5%
dithranol	ointment, 0.1%-2%
fluorouracil	ointment, 5%
■ podophyllum resin	solution, 10-25%
salicylic acid	solution 5%
urea	ointment or cream, 10%

13.6 Scabicides and pediculicides

■ benzyl benzoate	lotion, 25%
permethrin	cream 5%; lotion 1%

14. Diagnostic Agents

14.1 Ophthalmic medicines

fluorescein	eye drops, 1% (sodium salt)
■ tropicamide	eye drops, 0.5%

14.2 Radiocontrast media

■ amidotrizoate	injection, 140-420 mg iodine (as sodium or meglumine salt)/ml in 20-ml ampoule
barium sulfate	aqueous suspension
■ iohexol	injection 140–350 mg iodine/ml in 5-ml, 10-ml and 20-ml ampoule
■ iopanoic acid	tablet, 500 mg
■ propyliodone	oily suspension, 500-600 mg/ml in 20-ml ampoule *For administration only into the bronchial tree.*

Complementary List

■ *meglumine iotroxate* solution, 5-8 g iodine in 100-250 ml

15. Disinfectants and antiseptics

15.1 Antiseptics

■ chlorhexidine solution, 5% (digluconate) for dilution

■ ethanol solution, 70% (denatured)

■ polyvidone iodine solution, 10%

15.2 Disinfectants

■ chlorine base compound powder (0.1% available chlorine) for solution

■ chloroxylenol solution, 4.8%

glutaral solution, 2%

16. Diuretics

amiloride tablet, 5 mg (hydrochloride)

■ furosemide tablet, 40 mg; injection, 10 mg/ml in 2-ml ampoule

■ hydrochlorothiazide scored tablet, 25 mg

mannitol injectable solution, 10%, 20%

spironolactone tablet, 25 mg

17. Gastrointestinal medicines

17.1 Antacids and other antiulcer medicines

aluminium hydroxide tablet, 500 mg; oral suspension, 320 mg/5 ml

■ ranitidine tablet, 150 mg (as hydrochloride); oral solution 75 mg/5-ml; injection, 25 mg/ml in 2-ml ampoule

magnesium hydroxide oral suspension, equivalent to 550 mg magnesium oxide/10 ml

17.2 Antiemetic medicines

metoclopramide tablet, 10 mg (hydrochloride); injection, 5 mg (hydrochloride)/ml in 2-ml ampoule

promethazine tablet, 10 mg, 25 mg (hydrochloride); elixir or syrup, 5 mg (hydrochloride)/5 ml; injection, 25 mg (hydrochloride)/ml in 2-ml ampoule

17.3 Anti-inflammatory medicines

■ sulfasalazine tablet, 500 mg; suppository 500 mg; retention enema

Complementary List

■ *hydrocortisone* *suppository 25 mg (acetate); retention enema*

(the ■ only applies to hydrocortisone retention enema)

17.4 Laxatives

■ senna tablet, 7.5 mg (sennosides) (or traditional dosage forms)

17.5 Medicines used in diarrhoea

17.5.1 Oral rehydration

oral rehydration salts * (for glucose-electrolyte solution)

glucose:	75 mEq
sodium:	75 mEq or mmol/l
chloride:	65 mEq or mmol/l
potassium:	20 mEq or mmol/l
citrate:	10 mmol/l
osmolarity:	245 mOsm/l
glucose:	13.5 g/l
sodium chloride:	2.6 g/l
potassium chloride:	1.5 g/l
trisodium citrate dihydrate+:	2.9 g/l

+ trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/l. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use.

** in cases of cholera a higher concentration of sodium may be required.*

17.5.2 Medicines for diarrhoea in children

zinc sulfate* tablet or syrup in 10 mg per unit dosage forms

** in acute diarrhoea zinc sulphate should be used as an adjunct to oral rehydration salts.*

17.5.3 Antidiarrhoeal (symptomatic) medicines in adults

codeine* tablet, 30 mg (phosphate)

** the therapeutic efficacy of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.*

18. Hormones, other endocrine medicines and contraceptives

18.1 Adrenal hormones and synthetic substitutes

Addison's disease is a rare condition; adrenal hormones are already included in section 3.

18.2 Androgens

Complementary List

testosterone	injection, 200 mg (enantate) in 1-ml ampoule

18.3 Contraceptives

This subsection will be reviewed at the next meeting of the Expert Committee.

18.3.1 Oral hormonal contraceptives

■ ethinylestradiol + levonorgestrel	tablet, 30 micrograms + 150 micrograms
■ ethinylestradiol + norethisterone	tablet, 35 micrograms + 1.0 mg
levonorgestrel	tablet, 30 micrograms, 750 micrograms (pack of two), 1.5 mg

18.3.2 Injectable hormonal contraceptives

medroxyprogesterone acetate	depot injection, 150 mg/ml in 1-ml vial
norethisterone enantate	oily solution, 200 mg/ml in 1-ml ampoule

18.3.3 Intrauterine devices

copper-containing device

18.3.4 Barrier methods

condoms

diaphragms

18.4 Estrogens

■ ethinylestradiol*	tablet, 10 micrograms, 50 micrograms

** the public health relevance and/or comparative efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.*

18.5 Insulins and other antidiabetic agents

glibenclamide	tablet, 2.5 mg, 5 mg
insulin injection (soluble)	injection, 40 IU/ml in 10-ml vial, 100 IU/ml in 10-ml vial
intermediate-acting insulin	injection, 40 IU/ml in 10 ml vial; 100 IU/ml in 10 ml vial (as compound insulin zinc suspension or isophane insulin)
metformin	tablet, 500 mg (hydrochloride)

18.6 Ovulation inducers

Complementary List

clomifene	*tablet, 50 mg (citrate)*

18.7 Progestogens

norethisterone*	tablet, 5 mg

** the public health relevance and/or comparative efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.*

Complementary List

*medroxyprogesterone acetate**	*tablet, 5 mg*

** the public health relevance and/or comparative efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.*

18.8 Thyroid hormones and antithyroid medicines

levothyroxine	tablet, 50 micrograms, 100 micrograms (sodium salt)
potassium iodide	tablet, 60 mg
■ propylthiouracil	tablet, 50 mg

19. Immunologicals

19.1 Diagnostic agents

All tuberculins should comply with the WHO Requirements for Tuberculins (Revised 1985). WHO Expert Committee on Biological Standardization Thirty-sixth report, (WHO Technical Report Series, No. 745, 1987, Annex 1).

tuberculin, purified protein derivative (PPD)	injection

19.2 Sera and immunoglobulins

All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). WHO Expert Committee on Biological Standardization Forty-third report, (WHO Technical Report Series, No. 840, 1994, Annex 2).

anti-D immunoglobulin (human)	injection, 250 micrograms in single-dose vial

antitetanus immunoglobulin (human)	injection, 500 IU in vial
antivenom serum*	injection

** exact type to be defined locally*

diphtheria antitoxin	injection, 10 000 IU, 20 000 IU in vial
■ rabies immunoglobulin	injection, 150 IU/ml in vial

19.3 Vaccines

All vaccines should comply with the WHO Requirements for Biological Substances.

19.3.1 For universal immunization

BCG vaccine

diphtheria vaccine

hepatitis B vaccine

measles vaccine

pertussis vaccine

poliomyelitis vaccine

tetanus vaccine

19.3.2 For specific groups of individuals

influenza vaccine

meningococcal meningitis vaccine

mumps vaccine

rabies vaccine (inactivated: prepared in cell culture)

rubella vaccine

typhoid vaccine

yellow fever vaccine

20. Muscle relaxants (peripherally-acting) and cholinesterase inhibitors

■ alcuronium*	injection, 5 mg (chloride)/ml in 2-ml ampoule

** It is likely that alcuronium will be replaced and that similar products, including atracurium and/or pancuronium, will be added at the next meeting of the Expert Committee.*

neostigmine	tablet, 15 mg (bromide); injection, 500 micrograms in 1-ml ampoule; 2.5 mg (metilsulfate) in 1-ml ampoule
suxamethonium	injection, 50 mg (chloride)/ml in 2-ml ampoule; powder for injection (chloride), in vial

Complementary List

pyridostigmine	*tablet, 60 mg (bromide); injection, 1 mg in 1-ml ampoule*
■ *vecuronium*	*powder for injection, 10 mg (bromide) in vial*

21. Ophthalmalogical preparations

This section will be reviewed at the next meeting of the Expert Committee.

21.1 Anti-infective agents

■ gentamicin *	solution (eye drops), 0.3% (sulfate)

* final selection depends on indication for use.

■ idoxuridine	solution (eye drops), 0.1%; eye ointment, 0.2%
■ tetracycline	eye ointment, 1% (hydrochloride)

21.2 Anti-inflammatory agents

■ prednisolone	solution (eye drops), 0.5% (sodium phosphate)

21.3 Local anaesthetics

■ tetracaine	solution (eye drops), 0.5% (hydrochloride)

21.4 Miotics and antiglaucoma medicines

acetazolamide	tablet, 250 mg
■ pilocarpine	solution (eye drops), 2%, 4% (hydrochloride or nitrate)
■ timolol	solution (eye drops), 0.25%, 0.5% (as maleate)

21.5 Mydriatics

atropine	solution (eye drops), 0.1%; 0.5%, 1% (sulfate)

Complementary List

epinephrine (adrenaline)	*solution (eye drops), 2% (as hydrochloride)*

22. Oxytocics and antioxytocics

22.1 Oxytocics

■ ergometrine	injection, 200 micrograms (hydrogen maleate) in 1-ml ampoule

oxytocin	injection, 10 IU in 1-ml ampoule

Complementary List

misoprostol	*vaginal tablet, 25 micrograms*
mifepristone-misoprostol **	*tablet 200 mg - tablet 200 micrograms*

** requires close medical supervision.*

Where permitted under national law and where culturally acceptable.

22.2 Antioxytocics

nifedipine	immediate release capsule, 10 mg

23. Peritoneal dialysis solution

Complementary List

intraperitoneal dialysis solution (of appropriate composition)	*parenteral solution*

24. Psychotherapeutic medicines

24.1 Medicines used in psychotic disorders

■ chlorpromazine	tablet, 100 mg (hydrochloride); syrup, 25 mg (hydrochloride)/5ml; injection, 25 mg (hydrochloride)/ml in 2-ml ampoule
■ fluphenazine	injection, 25 mg (decanoate or enantate) in 1-ml ampoule
■ haloperidol	tablet, 2 mg, 5 mg; injection, 5 mg in 1-ml ampoule

24.2 Medicines used in mood disorders

24.2.1 Medicines used in depressive disorders

■ amitriptyline	tablet, 25 mg (hydrochloride)

24.2.2 Medicines used in bipolar disorders

carbamazepine	scored tablet, 100 mg, 200 mg
lithium carbonate	capsule or tablet, 300 mg
valproic acid	enteric coated tablet, 200 mg, 500 mg (sodium salt)

24.3 Medicines used in generalized anxiety and sleep disorders

■ diazepam	scored tablet, 2 mg, 5 mg

24.4 Medicines used for obsessive compulsive disorders and panic attacks

clomipramine	capsules, 10 mg, 25 mg (hydrochloride)

24.5 Medicines used in substance dependence programmes

Complementary List

■ *methadone**	*oral solution 5 mg/5ml, 10 mg/5ml, concentrate for oral solution 5 mg/ml, 10 mg/ml (hydrochloride)*

** the square box is added to include buprenorphine. The medicines should only be used within an established support programme.*

25. Medicines acting on the respiratory tract

25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease

■ beclometasone	inhalation (aerosol), 50 micrograms per dose (dipropionate); 250 micrograms (dipropionate) per dose
epinephrine (adrenaline)	injection, 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule
ipratropium bromide	inhalation (aerosol), 20 micrograms/metered dose
■ salbutamol	tablet, 2 mg, 4 mg (as sulfate); inhalation (aerosol), 100 micrograms (as sulfate) per dose; syrup, 2 mg/5 ml; injection, 50 micrograms (as sulfate)/ml in 5-ml ampoule; respirator solution for use in nebulizers, 5 mg (as sulfate)/ml

26. Solutions correcting water, electrolyte and acid–base disturbances

26.1 Oral

oral rehydration salts (for glucose-electrolyte solution)	see section 17.5.1
potassium chloride	powder for solution

26.2 Parenteral

glucose	injectable solution, 5%, 10% isotonic; 50% hypertonic

glucose with sodium chloride	injectable solution, 4% glucose, 0.18% sodium chloride (equivalent to Na^+ 30 mmol/l, Cl^- 30 mmol/l)
potassium chloride	solution, 11.2% in 20-ml ampoule, (equivalent to K^+ 1.5 mmol/ml, Cl^- 1.5 mmol/ml)
sodium chloride	injectable solution, 0.9% isotonic (equivalent to Na^+ 154 mmol/l, Cl^- 154 mmol/l
sodium hydrogen carbonate	injectable solution, 1.4% isotonic (equivalent to Na^+ 167 mmol/l, HCO_3^- 167 mmol/l); solution, 8.4% in 10-ml ampoule (equivalent to Na^+ 1000 mmol/l, HCO_3^- 1000 mmol/l)
■ sodium lactate, compound solution	injectable solution

26.3 Miscellaneous

water for injection	2-ml, 5-ml, 10-ml ampoules

27. Vitamins and minerals

ascorbic acid	tablet, 50 mg
■ ergocalciferol	capsule or tablet, 1.25 mg (50 000 IU); oral solution, 250 micrograms/ml (10 000 IU/ml)
iodine	iodized oil, 1 ml (480 mg iodine), 0.5 ml (240 mg iodine) in ampoule (oral or injectable); 0.57 ml (308 mg iodine) in dispenser bottle; capsule, 200 mg
■ nicotinamide	tablet, 50 mg
pyridoxine	tablet, 25 mg (hydrochloride)
retinol	sugar-coated tablet, 10 000 IU (as palmitate) (5.5 mg); capsule, 200 000 IU (as palmitate) (110 mg); oral oily solution 100 000 IU (as palmitate)/ml in multidose dispenser; water-miscible injection 100 000 IU (as palmitate) (55 mg) in 2-ml ampoule
riboflavin	tablet, 5 mg
sodium fluoride	in any appropriate topical formulation
thiamine	tablet, 50 mg (hydrochloride)

Complementary List

calcium gluconate	*injection, 100 mg/ml in 10-ml ampoule*

Access to Medicines

Intellectual property protection: impact on public health

The World Trade Organization (WTO) is an international organization of 148 Member countries dealing with the rules of trade. In joining the WTO, Members adhere to specific agreements. Of these agreements, Trade-Related Aspects of Intellectual Property Rights (TRIPS) establishes minimum standards for a set of intellectual property rights that WTO members institute through national legislation. It also contains provisions that allow a degree of flexibility and sufficient room for countries to accommodate their own patent and intellectual property systems and developmental needs. Patents on medicines have been one of the most hotly-debated topics since the adoption of the TRIPS Agreement because patents grant exclusivity for the duration of the patent term and result in patent holders having control over the production, supply, distribution and, by virtue of exclusivity, price.

It is argued that patents are crucial for pharmaceutical innovation and that without them there will be no financial incentive to fund the costs of discovery and development of new medicines. However, medicines prices in developing countries are often well above production costs. Developing countries account for a very small fraction of the global pharmaceutical market and the generation of income to fund more research and development is not dependent on profit from these markets. Indeed, until now, the patent protection system has provided very little incentive for research and development of new medicines needed for diseases afflicting developing countries and highlights the ineffectiveness of relying solely on the private sector to develop essential medicines. In many countries where payment for pharmaceuticals is “out-of-pocket” and health insurance is rare, escalating and unrealistic prices play a central role in denying access to patients of life-saving medicines.

Public health principles, in the context of access to medicines, are supported by a range of national and international legal and policy instruments, including the Constitution of the World Health Organization (WHO). From a human rights perspective, implementation of intellectual property rules should be governed by those principles which support public health goals and access to medicines, thus ensuring:

- a rapid and effective response to public health needs and crises;
- supply of quality medicines at affordable prices;
- effective competition through a multiplicity of potential suppliers;
- the provision for a wide range of pharmaceuticals to meet the basic health needs of the population; and
- equality of opportunities for countries in need, irrespective of their membership in the WTO, level of technological capacity, or lack of manufacturing capacity.

In 2001, World Trade Organization (WTO) members drew up the Doha Declaration to clarify ambiguities between the need for governments to apply the principles of public health and the terms of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). In particular, concerns had been growing that patent rules might restrict access to affordable medicines for populations in developing countries in their efforts to control diseases of public health importance, such as HIV, tuberculosis and malaria.

Although the impact of intellectual property on access to affordable medicines predated the TRIPS Agreement, the impending expiry of deadlines for implementing the TRIPS Agreement by developing countries has added impetus to the debate. Legal

challenges by the pharmaceutical industry to legislation enabling parallel imports of medicines, and provisions enacted on compulsory licences, highlighted the differing interpretations of the TRIPS Agreement obligations. That this was taking place against the backdrop of the HIV/AIDS pandemic afflicting the developing world further fuelled the need to focus international public attention on the manner in which intellectual property protection impacted areas of public health.

Affordability of essential medicines

The HIV pandemic and consequent urgency to make treatment available for millions of people brought to the fore the issue of affordability of antiretroviral therapy. When patent-protected antiretroviral treatments were first introduced, the cost was over US$ 10 000 per patient per year, putting them out of reach of the vast majority of HIV patients in developing countries where over three billion people live on less than US$ 2 a day. Although efforts have been made to reduce prices by pharmaceutical companies, including proposed donation programmes or heavy discounts, the scale of the crisis in developing countries clearly demanded a more systematic and sustainable strategy.

The announcement in 2001, by a pharmaceutical manufacturer to supply a generic version of antiretroviral triple therapy at US$ 350 per patient per year, together with the subsequent entry of other generic manufacturers into the arena, has brought about market competition resulting in significant reductions in prices of antiretroviral therapy. Additionally, there has been increased reliance on low-cost generic antiretroviral therapy as a strategy for treating patients in developing countries.

However, a debate continues on the comparative relevance of patents in determining access to medicines. The pharmaceutical industry underscores the importance of effective patent protection as an incentive for continued investment in the discovery and development of medicines. While it is not denied that the patent system provides incentives for pharmaceutical innovation, the market exclusivity conferred by patents leads to company profits that often outstrip the associated research, development and production costs altogether. The patent system has also not provided sufficient incentive for research and development of new medicines needed for diseases that afflict public health, including neglected diseases and orphan drugs, because forecasts deem the market too small or commercially unattractive.

In many developing countries, the current concern is how adoption of intellectual property regimes as required under the TRIPS Agreement can be balanced with efforts to maintain public health treatment programmes while boosting multiple sources of pharmaceuticals and controlling cost.

Although patent protection systems for pharmaceutical products are available in most developing countries, multinational companies have not patented their products in all of them. This may be because companies may not think it worth the expense to obtain and maintain patent protection in countries where the market is small and the risk of infringement low. The prevalence of patents is

Public health crisis management and patents

Anthrax

At the height of the Doha negotiations, mysterious anthrax attacks were causing panic in the USA, and health authorities began building stockpiles of ciprofloxazine to treat exposure. Concerns about the price and the patent holder's ability to produce adequate quantities of ciprofloxazine to protect its citizens led US and Canadian authorities to consider granting compulsory licences for generic production. In the event, significant price reductions and guaranteed supplies were finally negotiated with the manufacturer.[1]

Avian flu

Current concerns of a possible avian flu pandemic are now raising similar questions on the need for access to antivirals. As countries work out plans to prevent a human flu outbreak, the question of cost and availability of existing treatments under patent is once again being balanced with the need to call on public health measures to contain a highy pathogenic disease and ensure adequate protection of populations.[2]

[1] t'Hoen, E. TRIPS, pharmaceutical patents and access to medicines: Seattle, Doha and beyond. *Chicago Journal of International Law*, 2002; **31**(1).

[2] Tsang, KWT. H5N1 influenza pandemic: contingency plans. *Lancet*, 2005; **366**:533–534.

often higher in countries where a substantial market and technological capacity exists. None the less, even if patents do not exist for particular products and countries, the patent system may still have an effect on access to medicines. The existence of patents in potential supplier countries may allow the patentee to prevent supplies being exported to another country. This is why companies may patent selectively in countries that are potential suppliers.

Key provisions of TRIPS

Generic production is possible for the great majority of essential medicines, since they are currently not protected by patents in developing countries. However, this is not true for new medicines.

The TRIPS Agreement introduced global minimum standards for protecting and enforcing nearly all forms of intellectual property rights (IPR), including those for patents. International conventions prior to TRIPS did not specify minimum standards for patents. At the time that negotiations began, over 40 countries in the world did not grant patent protection for pharmaceutical products. The TRIPS Agreement now requires all WTO members, with few exceptions, to adapt their laws to the minimum standards of IPR protection. In addition to the minimum protection standards, the TRIPS Agreement also introduced detailed obligations on the enforcement of intellectual property rights.

Patent protection

The TRIPS Agreement requires WTO Members to provide protection for a minimum term of 20 years from the filing date of a patent application for any invention including for a pharmaceutical product or process. Prior to the TRIPS Agreement, patent duration was significantly shorter in many countries. For example, both developed and developing countries provided for patent terms ranging from 15 to 17 years, whilst in a number of developing countries like India, patents were granted for shorter terms of 5 to 7 years.

The TRIPS Agreement also requires countries to provide patent protection for both processes and products, in all fields of technology. Before TRIPS, many countries provided only process — but not product — patents. Product patents provide for absolute protection of the product, whereas process patents provide protection in respect of the technology and the process or method of manufacture. Protection for process patents would not prevent the manufacture of patented products by a process of reverse engineering, where a different process or method from that which has been invented (and patented) is used. For example, national legislation requiring only process patent protection has enabled manufacturers in certain countries to make generic versions of patented medicines. These countries have opted to make use of the transition period that permitted countries to delay, until 2005, patent protection in the areas of technology that had not been so protected before the TRIPS Agreement. (See transition periods below).

Protection of data submitted for the registration of pharmaceuticals

As a condition for permitting the sale or marketing of a pharmaceutical product, drug regulatory authorities require pharmaceutical companies to submit data demonstrating the safety, quality and efficacy of the product. The TRIPS Agreement requires that WTO Members protect undisclosed test data, submitted to drug regulatory authorities for the purposes of obtaining marketing approval, against unfair commercial use. Since countries have considerable discretion to define “unfair commercial use”, it is argued that countries can meet their obligations to protect test data by prohibiting “dishonest” use of data. Use by government authorities to assess the efficacy and toxicity of a pharmaceutical would not be affected, in this case. However, it is now argued that data exclusivity is a requirement of the TRIPS Agreement. The data exclusivity approach grants the originator exclusive rights over their test data and prevents regulatory authorities from relying on the test data to register generic substitutes.

Prior to the TRIPS Agreement coming into force, most countries allowed reliance on originator test data to approve generic products. Once test data was submitted by the originator company, the regulatory authorities could rely on the data to approve subsequent applications on similar products, or to rely on proof of prior approval of a similar product in another country. Generic manufacturers need only to prove that their product is chemically identical to the brand-name, original product, and in some countries, that it is bioequivalent. This approach enabled swift introduction of generics into the market without registration data-related costs. Within the data exclusivity approach, once a company has submitted original test data, no competing manufacturer is allowed to rely on these data for a period of time.

Data exclusivity could thus pose an obstacle to effective use of compulsory licences, as the entry of the generic product would be delayed for the duration of the exclusivity period or for the time it takes to undertake a new compilation of test data. The public interest in limiting data protection is to promote competition and ensure that data protection does not become the means to block timely entrance of affordable generic medicines of public health importance.

Transition periods

The TRIPS Agreement provides for transition periods, permitting developing countries additional time to bring national legislation and practices into conformity with TRIPS provisions. There are three main transition periods. First was the 1995–2000 transition period, at the end of which countries were required to implement the TRIPS Agreement. The 2000–2005 transition period allowed certain countries to delay providing product patent protection in the areas of technology that had not been so protected at the time of the TRIPS Agreement coming into operation in that country. These countries were allowed a further 5 years to put in place a product patent regime for pharmaceuticals and agro-chemicals. The third transition period allowed least-developed countries (LDCs) until 2006 to implement their obligations under the TRIPS Agreement in view of their economic, financial and administrative constraints. In addition, this period may still be extended by the TRIPS Council on request of an LDC Member. This transition period has been further extended to 2016 with respect to patents on pharmaceutical products and exclusive marketing rights by the Doha Declaration (see below).

The transition periods have meant that pharmaceuticals or medicines patented before developing countries implemented their TRIPS obligations will not receive patent protection, and thus generic competition is possible. Medicines patented after developing countries have implemented their TRIPS obligations are progressively coming onto the market and will constitute an increasing share of marketed medicines. A substantial change is expected after 2005, when all developing countries will be required to provide patent protection for pharmaceutical products and the mailbox patents are processed.

Public health considerations

The current minimum standards in the TRIPS Agreement — historically derived from those of developed countries — may not necessarily be appropriate for developing countries struggling to meet health and development needs. The new obligations have dramatically changed the legal framework for the production, supply and access to affordable medicines in developing countries.

The role of the Doha Declaration

Although the TRIPS Agreement affords considerable discretion on how its obligations are interpreted and implemented by governments, developing countries have faced obstacles when seeking to implement measures to promote access to affordable medicines. Thus, developing countries sought to clarify — through adoption of the Doha Declaration — that the provisions in the TRIPS Agreement did provide sufficient flexibility and discretion to ensure access to medicines in the interests of public health.

The Doha Declaration refers to several aspects of TRIPS, including the right to grant compulsory licenses and the freedom to determine the grounds upon which licences are granted, the right to determine what constitutes a national emergency and circumstances of extreme urgency, and the freedom to establish the regime of exhaustion of intellectual property rights. These are briefly described below.

The TRIPS Agreement allows the use of compulsory licences. Compulsory licensing enables a competent government authority to license the use of a patented invention to a third party or government agency without the consent of the patent-holder. Article 31 of the Agreement sets forth a number of conditions for the granting of compulsory licences. These include a case-by-case determination of compulsory licence applications, the need to demonstrate prior (unsuccessful) negotiations with the patent owner for a voluntary licence and the payment of adequate remuneration to the patent holder. Where compulsory licences are granted to address a national emergency or other circumstances of extreme urgency, certain requirements are waived in order to hasten the process, such as that for the need to have had prior negotiations to obtain a voluntary licence from the patent holder.

Although the Agreement refers to some of the possible grounds (such as emergency and anti-competitive practices) for issuing compulsory licences, it leaves Members full freedom to stipulate other grounds, such as those related to public health or public interest. The Doha Decla-

ration states that each Member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted.

Parallel importation is importation without the consent of the patent-holder of a patented product marketed in another country either by the patent holder or with the patent-holder's consent. The principle of exhaustion states that once patent holders have sold a patented product, they cannot prohibit the subsequent resale of that product since their rights in respect of that market have been exhausted by the act of selling the product. Article 6 of the TRIPS Agreement explicitly states that practices relating to parallel importation cannot be challenged under the WTO dispute settlement system. The Doha Declaration has reaffirmed that Members do have this right, stating that each Member is free to establish its own regime for such exhaustion without challenge .

Since many patented products are sold at different prices in different markets, the rationale for parallel importation is to enable the import of lower priced patented products. Parallel importing can be an important tool enabling access to affordable medicines because there are substantial price differences between the same pharmaceutical product sold in different markets.

Paragraph 6 of the Doha Declaration

Although existing provisions of the TRIPS Agreement permit the grant of compulsory licences to enable generic production of medicines, countries without domestic manufacturing capacity cannot avail themselves of this flexibility. The option of importing generic medicines is hampered by the restriction in the TRIPS Agreement that requires production under compulsory licence to be predominantly for the supply of the domestic market. This has raised concern that exporting countries may have difficulties exporting sufficient quantities to meet the needs of those countries with insufficient or no manufacturing capacity. The WTO solution is essentially a waiver of the export restriction, thereby allowing the total amount of production under a compulsory licence to be exported. Whether countries may export and import generic versions of patented medicines under the system adopted in the WTO Decision will depend on the extent to which national laws allow for it.

A number of potential exporting countries have amended national laws to enable the production and export of generic medicines under compulsory license. Canada was the first country, followed subsequently by Norway. The European Union is currently considering its draft regulation. India, has also included a provision on compulsory licenses for production and export in the amendment of the patent law. However, there has not been any notification by countries to the WTO in respect of their intention to use the system as an importer. There may be a number of possible reasons for this. First, the threat of compulsory licensing for production of competing generics has led pharmaceutical companies to offer larger discounts. Secondly, the granting of compulsory licences under the system may appear to be too complex and burdensome for developing countries. In addition, there may not have been a need. Where there is no patent in force in the exporting country, production and export may take place without a compulsory licence. This has been the case with exports from India, where until recently, the absence of product patent protection enabled the production of generic versions of medicines. In the post-2005 environment, when almost all countries are obliged to provide product patent protection, the effectiveness of the WTO decision may well be put to the test.

Conclusion

The TRIPS Agreement does not prevent Members from allowing generic substitution. But if the wording and implementation of TRIPS-compliant national legislation and regulations are inappropriate the introduction of new generic drugs can be delayed. Prompt introduction of generic drugs can be facilitated by drafting appropriate legislation and regulations on patentability; use of exceptions to exclusive rights which permit early testing and approval of generics (including allowing access to pre-registration test data); and compulsory licensing.

Whilst the adoption of the Doha Declaration marked a watershed in the debate on intellectual property and access to medicines, there remain major challenges for developing countries to interpret and implement the TRIPS Agreement and other intellectual property rules in a manner supportive of their efforts to protect public health and promote access to medicines for all.

Next steps

It is vital for countries to be informed of their options in implementing the TRIPS Agreement. Through its technical cooperation programme, WHO can provide independent advice and

technical assistance to countries to help them develop informed approaches to addressing the health implications of trade and intellectual property devices.

WHO's focus is on awareness building for policy makers and independent evaluations of the health impact of international trade agreements for countries, leading to effective participation in international and regional negotiations. In this way, developing country needs and interests will be adequately taken into account.

WHO assistance will also include review of national health, pharmaceutical and intellectual property policies, legislation and practices, with a view to promoting the development and incorporation of TRIPS safeguards within the national policy and legal framework, followed by monitoring and analysis of access to essential medicines, including the impact of new trends and developments at the regional and bilateral levels.

References

1. World Trade organization http://www.wto.int

2. Department of Technical Cooperation for Essential Drugs and Traditional Medicine, World Health Organization http://www.who.int/medicines

The International Pharmacopoeia

International Pharmacopoeia: fourth edition in development

World Health Organization — The fourth edition of *The International Pharmacopoeia* is now in preparation. The main purpose of this new edition is to consolidate the five separate volumes of the current third edition and to include those new monographs for antiretrovirals that were adopted by the Expert Committee on Specifications for Pharmaceutical Preparations in October 2004. In preparing this consolidated edition, an opportunity has been taken to review the General notices of the *International Pharmacopoeia*. Certain additions and amendments have also been made to the notices in order to clarify interpretation and facilitate application of the requirements by the user. Certain aspects of the layout and format of the publication will be improved. In the fourth edition, all the monograph texts will be brought together in one section and the method texts in another. Each of these major sections will be divided into appropriate sub-sections and the method texts will be numbered for ease of cross-reference.

Oral rehydration salts

The current monograph for oral rehydration salts has been revised to conform to the modified formula published in the 13th Model List of Essential Medicines (WHO Technical Report Series, No. 920, 2003) and in the Model Formulary 2004. The revised formula has a reduced sodium chloride and glucose content providing a solution with a reduced osmolarity of 245 mOsm/l. Due to the improved effectiveness of the reduced osmolarity ORS solution, especially for children with acute, non-cholera diarrhoea, WHO and UNICEF now recommend that countries use and manufacture this formulation in place of the previously recommended ORS, i.e. the one published in the third edition of *The International Pharmacopoeia*, which has a total osmolarity of 311 mOsm/l.

Method texts that have been updated include, for example, the text on high performance liquid chromatography (HPLC). This has been revised to clarify certain technical terms and to add advice on adjustment of chromatographic conditions as recommended by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2004.

New monographs

Monographs for the following antiretrovirals will be published in the fourth edition of *The International Pharmacopoeia*: didanosine, indinavir sulfate, nelfinavir mesilate, nevirapine, ritonavir, saquinavir, saquinavir mesilate. The adopted texts for these monographs were published in Drug Information, Volume 19 Number 1 (http://www.who.int/druginformation/vol19num1 2005/19-1table of contents.shtml) and are also available on the WHO website at (http://www.who.int/medicines/organization/ qsm/activities/qualityassurance/pharmacopoeia/intpharmarvs.shtml). Meanwhile, work is continuing on the preparation of monographs for the associated dosage forms, for other antiretroviral substances and dosage forms and for fixed-dose combination products for the treatment of tuberculosis.

International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names: List 54

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [*Off. Rec. Wld Health Org.*, 1955, **60**, 3 (Resolution EB15.R7); 1969, **173**, 10 (Resolution EB43.R9)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.
Lists of Proposed (1–91) and Recommended (1–52) International Nonproprietary Names can be found in *Cumulative List No. 11, 2004* (available in CD-ROM only).

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES: Liste 54

Il est notifié que, conformément aux dispositions du paragraphe 7 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques [*Actes off. Org. mond. Santé*, 1955, **60**, 3 (résolution EB15.R7); 1969, **173**, 10 (résolution EB43.R9)] les dénominations ci-dessous sont choisies par l'Organisation mondiale de la Santé en tant que dénominations communes internationales recommandées. L'inclusion d'une dénomination dans les listes de DCI recommandées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.
On trouvera d'autres listes de Dénominations communes internationales proposées (1–91) et recommandées (1–52) dans la *Liste récapitulative No. 11, 2004* (disponible sur CD-ROM seulement).

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS: Lista 54

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 (1–91) y Recomendadas (1–52) se encuentran reunidas en *Cumulative List No. 11, 2004* (disponible sólo en CD-ROM).

Latin, English, French, Spanish: *Recommended INN*	*Chemical name or description; Molecular formula; Graphic formula*
DCI Recommandée	*Nom chimique ou description; Formule brute; Formule développée*
DCI Recomendada	*Nombre químico o descripción; Fórmula molecular; Fórmula desarrollada*

acidum salclobuzicum

salclobuzic acid

4-(4-chloro-2-hydroxybenzamido)butanoic acid

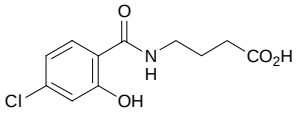
acide salclobuzique

acide 4-[(4-chloro-2-hydroxybenzoyl)amino]butanoïque

ácido salclobúzico

ácido 4-[(4-cloro-2-hidroxibenzoil)amino]butanoico

$C_{11}H_{12}ClNO_4$



ancrivirocum

ancriviroc

3-({4-[(*Z*)-(4-bromophenyl)(ethoxyimino)methyl]-4'-methyl-[1,4'-bipiperidin]-1'-yl}carbonyl)-2,4-dimethylpyridine-1-oxide

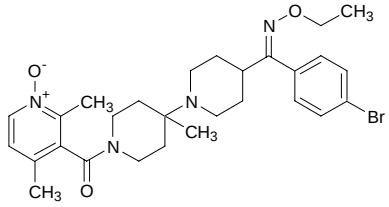
ancriviroc

4-[(*Z*)-(4-bromophényl)(éthoxyimino)méthyl]-1'-[(2,4-diméthyl-1-oxydopyridin-3-yl)carbonyl]-4'-méthyl-1,4'-bipipéridinyle

ancriviroc

4-[(*Z*)-(4-bromofenil)(etoxiimino)metil]-1'-[(2,4-dimetil-1-oxidopiridin-3-il)carbonil]-4'-metil-1,4'-bipipéridinilo

$C_{28}H_{37}BrN_4O_3$



aplindorum

aplindore

(2*S*)-2-[(benzylamino)methyl]-2,3,7,9-tetrahydro-8*H*-1,4-dioxino=[2,3-*e*]indol-8-one

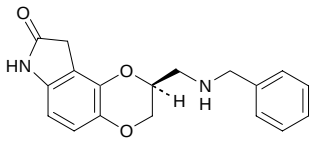
aplindore

(2*S*)-2-[(benzylamino)méthyl]-2,3,7,9-tétrahydro-8*H*-1,4-dioxino=[2,3-*e*]indol-8-one

aplindor

(2*S*)-2-[(bencilamino)metil]-2,3,7,9-tetrahidro-8*H*-1,4-dioxino=[2,3-*e*]indol-8-ona

$C_{18}H_{18}N_2O_3$



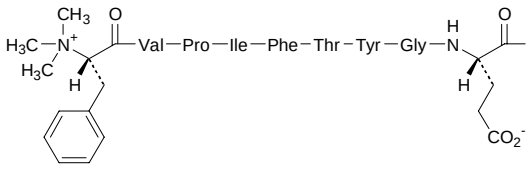
atilmotinum

atilmotin — *N*-[(2*S*)-3-phenyl-2-(trimethylazaniumyl)propanoyl]-L-valyl-L-prolyl-L-isoleucyl-L-phenylalanyl-L-threonyl-L-tyrosylglycyl-L-glutamyl-L-leucyl-L-glutaminyl-D-arginyl-L-leucyl-L-lysinamide

atilmotine — *N*-[(2*S*)-3-phényl-2-(triméthylammonio)propanoyl]-L-valyl-L-prolyl-L-isoleucyl-L-phénylalanyl-L-thréonyl-L-tyrosylglycyl-L-glutamyl-L-leucyl-L-glutaminyl-D-arginyl-L-leucyl-L-lysinamide

atilmotina — *N*-[(2*S*)-3-fenil-2-(trimetilamonio)propanoil]-L-valil-L-prolil-L-isoleucil-L-fenilalanil-L-treonil-L-tirosilglicil-L-glutamil-L-leucil-L-glutaminil-D-arginil-L-leucil-L-lisinamida

$C_{86}H_{134}N_{20}O_{19}$



Leu—Gln—D-Arg—Leu—Lys—NH_2

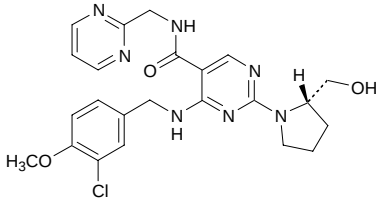
avanafilum

avanafil — 4-{[(3-chloro-4-methoxyphenyl)methyl]amino}-2-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]-*N*-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide

avanafil — 4-[(3-chloro-4-méthoxybenzyl)amino]-2-[(2*S*)-2-(hydroxyméthyl)=pyrrolidin-1-yl]-*N*-(pyrimidin-2-ylméthyl)pyrimidine-5-carboxamide

avanafilo — 4-[(3-cloro-4-metoxibencil)amino]-2-[(2*S*)-2-(hidroximetil)pirrolidin-1-il]-*N*-(pirimidin-2-ilmetil)pirimidina-5-carboxamida

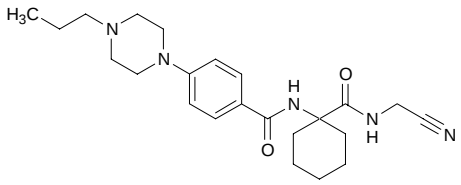
$C_{23}H_{26}ClN_7O_3$



balicatibum

balicatib	*N*-{1-[(cyanomethyl)carbamoyl]cyclohexyl}-4-(4-propylpiperazin-1-yl)benzamide
balicatib	*N*-[1-[(cyanométhyl)carbamoyl]cyclohexyl]-4-(4-propylpipérazin-1-yl)benzamide
balicatib	*N*-[1-[(cianometil)carbamoil]ciclohexil]-4-(4-propilpiperazin-1-il)benzamida

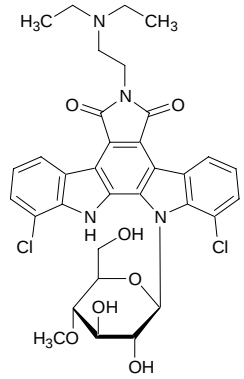
$C_{23}H_{33}N_5O_2$



becatecarinum

becatecarin	1,11-dichloro-6-[2-(diethylamino)ethyl]-12-(4-*O*-methyl-β-D-glucopyranosyl)-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo=[3,4-*c*]carbazole-5,7(6*H*)-dione
bécatécarine	1,11-dichloro-6-[2-(diéthylamino)éthyl]-12-(4-*O*-méthyl-β-D-glucopyranosyl)-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo=[3,4-*c*]carbazole-5,7(6*H*)-dione
becatecarina	1,11-dicloro-6-[2-(dietilamino)etil]-12-(4-*O*-metil-β-D-glucopiranosil)-12,13-dihidro-5*H*-indolo[2,3-*a*]pirrolo[3,4-*c*]carbazol-5,7(6*H*)-diona

$C_{33}H_{34}Cl_2N_4O_7$



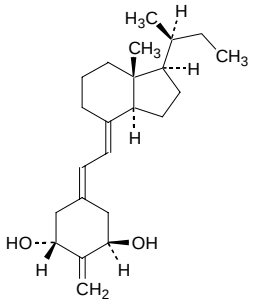
becocalcidiolum

becocalcidiol (1*R*,3*R*)-4-(2-{(1*R*,3a*S*,7a*R*)-1-[(2*S*)-butan-2-yl]-7a-methyloctahydro-4*H*-inden-4-ylidene}ethylidene)-2-methylidenecyclohexane-1,3-diol

bécocalcidiol (1*R*,3*R*)-2-méthylidène-5-[(2*E*)-2-[(1*R*,3a*S*,7a*R*)-7a-méthyl-1-[(1*S*)-1-méthylpropyl]octahydro-4*H*-indén-4-ylidène]éthylidène]= cyclohexane-1,3-diol

becocalcidiol (1*R*,3*R*)-2-metilideno-5-[(2*E*)-2-[(1*R*,3a*S*,7a*R*)-7a-metil-1-[(1*S*)-1-metilpropil]octahidro-4*H*-inden-4-ilideno]etilideno]= ciclohexano-1,3-diol

$C_{23}H_{36}O_2$



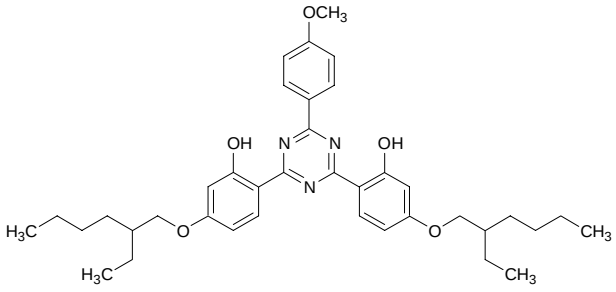
bemotrizinolum

bemotrizinol 2,2'-[6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diyl]bis={5-[(2-ethylhexyl)oxy]phenol}

bémotrizinol 2,2'-[6-(4-méthoxyphényl)-1,3,5-triazine-2,4-diyl]bis=[5-[(2-éthylhexyl)oxy]phénol]

bemotrizinol 2,2'-[6-(4-metoxifenil)-1,3,5-triazina-2,4-diil]bis[5-[(2-etilhexil)=oxi]fenol]

$C_{38}H_{49}N_3O_5$



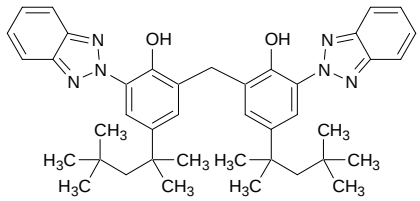
besilesomabum

besilesomab	immunoglobulin G1, anti-(human CEA (carcinoembryonic antigen)-related antigen) (mouse monoclonal BW 250/183 heavy chain), disulfide with mouse monoclonal BW 250/183 κ-chain, dimer
bésilésomab	immunoglobuline G1, anti-(molécules de l'adhésion cellulaire, antigènes carcinoembryonaires humains (CEA ou CD66)), dimère du disulfure entre la chaîne lourde et la chaîne κ de l'anticorps monoclonal de souris BW 250/183
besilesomab	inmunoglobulina G1, anti-(moléculas de adhesión celular, antígenos carcinoembrionarios humanos (CEA o CD66)), dímero del disulfuro entre la cadena pesada y la cadena κ del anticuerpo monoclonal de ratón BW 250/183

bisoctrizolum

bisoctrizole	2,2'-methylenebis[6-(2*H*-benzotriazol-2-yl)-4-(2,4,4-trimethylpentan-2-yl)phenol]
bisoctrizole	2,2'-méthylènebis[6-(2*H*-benzotriazol-2-yl)-4-(1,1,3,3-tétraméthylbutyl)phénol]
bisoctrizol	2,2'-metilenobis[6-(2*H*-benzotriazol-2-il)-4-(1,1,3,3-tetrametilbutil)=fenol]

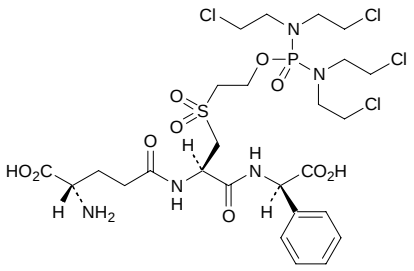
$C_{41}H_{50}N_6O_2$



canfosfamidum

canfosfamide	*N*-γ-L-glutaminyl-3-(2-{bis[bis(2-chloroethyl)amino]=phosphoryl}ethanesulfonyl)-L-alanyl-(2*R*)-2-phenylglycine
canfosfamide	acide (2*S*)-2-amino-5-[[(1*R*)-1-[[[2-[[bis[bis(2-chloroéthyl)amino]=phosphinoyl]oxy]éthyl]sulfonyl]méthyl]-2-[[(*R*)-carboxyphénylméthyl]=amino]-2-oxoéthyl]amino]-5-oxopentanoïque
canfosfamida	ácido (2*S*)-2-amino-5-[[(1*R*)-1-[[[2-[[bis[bis(2-cloroetil)amino]=fosfinoil]oxi]etil]sulfonil]metil]-2-[[(*R*)-carboxifenilmetil]amino]-2-oxoetil]amino]-5-oxopentanoico

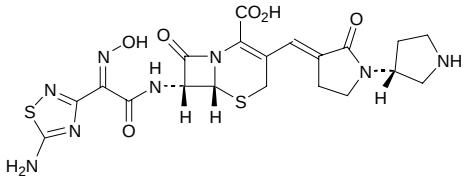
$C_{26}H_{40}Cl_4N_5O_{10}PS$



ceftobiprolum

ceftobiprole	(6*R*,7*R*)-7-[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(hydroxyimino)= acetamido]-8-oxo-3-[(*E*){(3'*R*)-2-oxo-[1,3'-bipyrrolidin]-3-ylidene}= methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
ceftobiprole	acide (6*R*,7*R*)-7-[[(2*Z*)-(5-amino-1,2,4-thiadiazol-3-yl)= (hydroxyimino)acétyl]amino]-8-oxo-3-[(*E*)-[(3'*R*)-2-oxo-1,3'-bipyrrolidinyl-3-ylidène]méthyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ène-2-carboxylique
ceftobiprol	ácido (6*R*,7*R*)-7-[[(2*Z*)-(5-amino-1,2,4-tiadiazol-3-il)(hidroxiimino)= acetil]amino]-8-oxo-3-[(*E*)-[(3'*R*)-2-oxo-1,3'-bipirrolidinil-3-ilideno]metil]-5-tia-1-azabiciclo[4.2.0]oct-2-eno-2-carboxílico

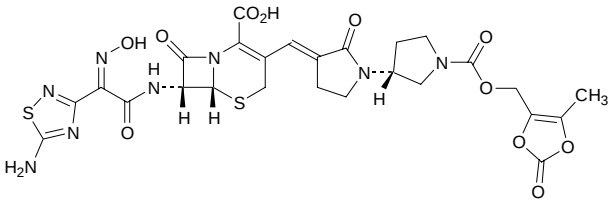
$C_{20}H_{22}N_8O_6S_2$



ceftobiprolum medocarilum

ceftobiprole medocaril	(6*R*,7*R*)-7-[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(hydroxyimino)= acetamido]-3-[(*E*){(3'*R*)-1'-[(5-methyl-2-oxo-1,3-dioxol-4-yl)= methoxycarbonyl]-2-oxo-[1,3'-bipyrrolidin]-3-ylidene}methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
ceftobiprole médocaril	acide (6*R*,7*R*)-7-[[(2*Z*)-(5-amino-1,2,4-thiadiazol-3-yl)= (hydroxyimino)acétyl]amino]-3-[(*E*)-[(3'*R*)-1'-[[(5-méthyl-2-oxo-1,3-dioxol-4-yl)méthoxy]carbonyl]-2-oxo-1,3'-bipyrrolidinyl-3-ylidène]méthyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ène-2-carboxylique
ceftobiprol medocarilo	ácido (6*R*,7*R*)-7-[(2*Z*)-(5-amino-1,2,4-tiadiazol-3-il)(hidroxiimino)= acetamido]-3-[(*E*)-[(3'*R*)-1'-[[(5-metil-2-oxo-1,3-dioxol-4-il)metoxi]carbonil]-2-oxo-1,3'-bipirrolidinil-3-ilideno]metil]-8-oxo-5-tia-1-azabiciclo[4.2.0]oct-2-eno-2-carboxílico

$C_{26}H_{26}N_8O_{11}S_2$



cintredekinum besudotoxum

cintredekin besudotox — toxin hIL13-PE38QQR (plasmid phuIL13-Tx)

cintrédékine bésudotox — [Met^{17},His^{18}]précurseur de l'interleukine-13 humaine-(17-132)-peptide (132→246')-protéine avec la dès-Ala^{365},Asp^{366},Val^{367},Val^{368},Ser^{369},Leu^{370},Thr^{371},Cys^{372},Pro^{373},Val^{374},Ala^{375},Ala^{376},Gly^{377},Glu^{378},Cys^{379},Ala^{380}-[Lys^{246},Ala^{247},Ser^{248},Gly^{249},Gly^{250},Asn^{364},Val^{407},Ser^{515},Gln^{590},Gln^{606},Arg^{613}]exotoxine A (*Pseudomonas aeruginosa*)-(246-613)-peptide

cintredekina besudotox — toxina hIL13-PE38QQR (plásmido phuIL13-Tx)

$C_{2234}H_{3512}N_{650}O_{682}S_{10}$

```
MHSPGPVPPS TALRELIEEL VNITQNQKAP LCNGSMVWSI
NLTAGMYCAA LESLINVSGC SAIEKTQRML SGFCPHKVSA
GQFSSLHVRD TKIEVAQFVK DLLLHLKKLF REGRFNKASG
GPEGGSLAAL TAHQACHLPL ETFTRHRQPR GWEQLEQCGY
PVQRLVALYL AARLSWNQVD QVIRNALASP GSGGDLGEAI
REQPEQARLA LTLAAAESER FVRQGTGNDE AGAANGPADS
GDALLERNYP TGAEFLGDGG DVSFSTRGTQ NWTVERLLQA
HRQLEERGYV FVGYHGTFLE AAQSIVFGGV RARSQDLDAI
WRGFYIAGDP ALAYGYAQDQ EPDARGRIRN GALLRVYVPR
SSLPGFYRTS LTLAAPEAAG EVERLIGHPL PLRLDAITGP
EEEGGRLETI LGWPLAERTV VIPSAIPTDP RNVGGDLDPS
SIPDQEQAIS ALPDYASQPG QPPREDLR
```

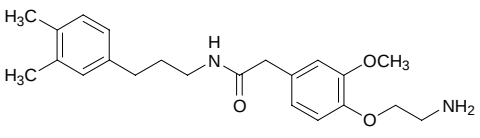
davasaicinum

davasaicin — 2-[4-(2-aminoethoxy)-3-methoxyphenyl]-*N*-[3-(3,4-dimethylphenyl)=propyl]acetamide

davasaïcine — 2-[4-(2-aminoéthoxy)-3-méthoxyphényl]-*N*-[3-(3,4-diméthylphényl)=propyl]acétamide

davasaicina — 2-[4-(2-aminoetoxi)-3-metoxifenil]-*N*-[3-(3,4-dimetilfenil)propil]=acetamida

$C_{22}H_{30}N_2O_3$



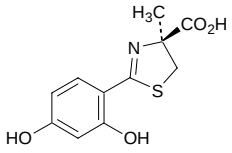
deferitrinum

deferitrin — (4*S*)-2-(2,4-dihydroxyphenyl)-4-methyl-4,5-dihydro-1,3-thiazole-4-carboxylic acid

déféritrine — acide (+)-(4*S*)-2-(2,4-dihydroxyphényl)-4-méthyl-4,5-dihydrothiazole-4-carboxylique

deferitrina — ácido (+)-(4*S*)-2-(2,4-dihidroxifenil)-4-metil-4,5-dihidrotiazol-4-carboxílico

$C_{11}H_{11}NO_4S$



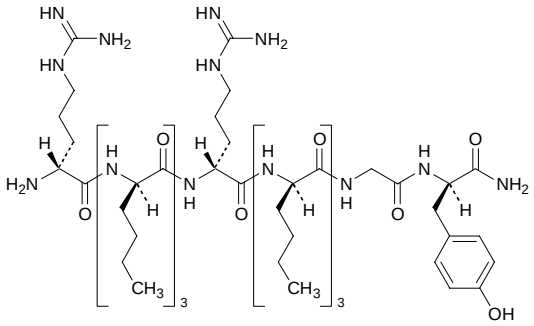
delmitidum

delmitide — (2*R*)-2-[(2*R*)-2-{(2*R*)-2-[(2*R*)-2-{(2*R*)-2-[(2*R*)-2-(D-arginylamino)=hexanamido]hexanamido}hexanoyl-D-arginylamino]=hexanamido}hexanamido]hexanoylglycyl-D-tyrosinamide

delmitide — D-arginyl-(2*R*)-2-aminohexanoyl-(2*R*)-2-aminohexanoyl-(2*R*)-2-aminohexanoyl-D-arginyl-(2*R*)-2-aminohexanoyl-(2*R*)-2-aminohexanoyl-(2*R*)-2-aminohexanoylglycyl-D-tyrosinamide

delmitida — D-arginil-(2*R*)-2-aminohexanoil-(2*R*)-2-aminohexanoil-(2*R*)-2-aminohexanoil-D-arginil-(2*R*)-2-aminohexanoil-(2*R*)-2-aminohexanoil-(2*R*)-2-aminohexanoilglicil-D-tirosinamida

$C_{59}H_{105}N_{17}O_{11}$



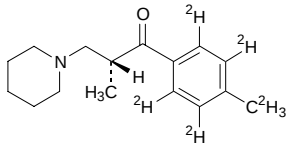
deutolperisonum

deutolperisone — 2-methyl-1-{4-([$^2H_3$]methyl)[2,3,5,6-$^2H_4$]phenyl}-3-(piperidin-1-yl)propan-1-one

deutolpérisone — (2*RS*)-2-méthyl-1-(4-($^2H_3$)méthyl(2,3,5,6-$^2H_4$)phényl)-3-(pipéridin-1-yl)propan-1-one

deutolperisona — (2*RS*)-2-metil-1-(4-[$^2H_3$]metil[2,3,5,6-$^2H_4$]fenil)-3-(piperidin-1-il)propan-1-ona

$C_{16}H_{16}{}^{2}H_{7}NO$



and enantiomer
et énantiomère
y enantiómero

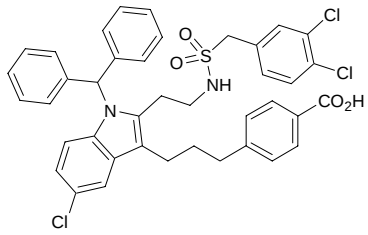
efipladibum

efipladib — 4-(3-{5-chloro-2-[2-({[(3,4-dichlorophenyl)methyl]sulfonyl}amino)=ethyl]-1-(diphenylmethyl)-1*H*-indol-3-yl}propyl)benzoic acid

éfipladib — acide 4-[3-[5-chloro-2-[2-[[(3,4-dichlorobenzyl)sulfonyl]amino]éthyl]-1-(diphénylméthyl)-1*H*-indol-3-yl]propyl]benzoïque

efipladib — ácido 4-[3-[5-cloro-2-[2-[[(3,4-diclorobencil)sulfonil]amino]etil]-1-(difenilmetil)-1*H*-indol-3-il]propil]benzoico

$C_{40}H_{35}Cl_3N_2O_4S$



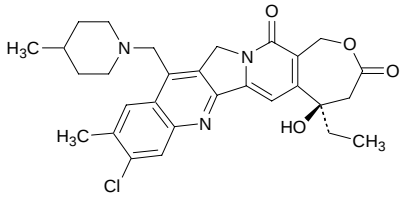
elomotecanum

elomotecan — (5*R*)-9-chloro-5-ethyl-5-hydroxy-10-methyl-12-[(4-methylpiperidin-1-yl)methyl]-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]=indolizino[1,2-*b*]quinoline-3,15-dione

élomotécan — (5*R*)-9-chloro-5-éthyl-5-hydroxy-10-méthyl-12-[(4-méthylpipéridin-1-yl)méthyl]-1,4,5,13-tétrahydro-3*H*,15*H*-oxépino[3',4':6,7]=indolizino[1,2-*b*]quinoléine-3,15-dione

elomotecán — (5*R*)-9-cloro-5-etil-5-hidroxi-10-metil-12-[(4-metilpiperidin-1-il)metil]-1,4,5,13-tetrahidro-3*H*,15*H*-oxepino[3',4':6,7]indolizino=[1,2-*b*]quinolina-3,15-diona

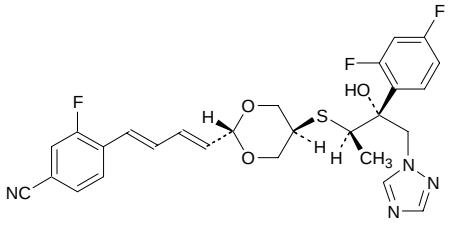
$C_{29}H_{32}ClN_3O_4$



embeconazolum

embeconazole	4-{(1*E*,3*E*)-4-(*trans*-5-{[(2*R*,3*R*)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)butan-2-yl]sulfanyl}-1,3-dioxan-2-yl)buta-1,3-dien-1-yl}-3-fluorobenzonitrile
embéconazole	(-)-4-[(1*E*,3*E*)-4-[*trans*-5-[[(1*R*,2*R*)-2-(2,4-difluorophényl)-2-hydroxy-1-méthyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]sulfanyl]-1,3-dioxan-2-yl]buta-1,3-diényl]-3-fluorobenzonitrile
embeconazol	(-)-4-[(1*E*,3*E*)-4-[*trans*-5-[[(1*R*,2*R*)-2-(2,4-difluorofenil)-2-hidroxi-1-metil-3-(1*H*-1,2,4-triazol-1-il)propil]sulfanil]-1,3-dioxan-2-il]buta-1,3-dienil]-3-fluorobenzonitrilo

$C_{27}H_{25}F_3N_4O_3S$



epoetinum zeta

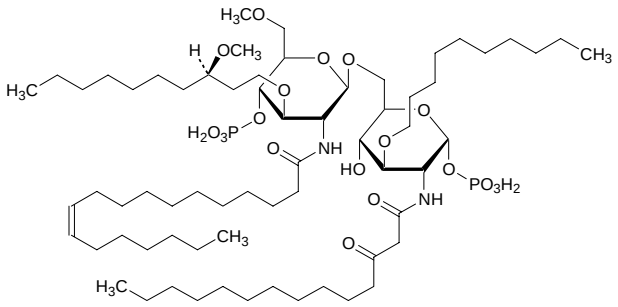
epoetin zeta	1-165-erythropoietin (human clone B03XA01), glycoform ζ
époétine zêta	1-165-érythropoïétine (humaine B03XA01), glycoforme ζ
epoetina zeta	1-165-eritropoyetina (humana B03XA01), glicoforma ζ

$C_{809}H_{1301}N_{229}O_{240}S_5$

eritoranum

eritoran	2-deoxy-3-*O*-[(3*R*)-3-methoxydecyl]-6-*O*-methyl-2-(octadec-11-enamido)-4-*O*-phosphono-β-D-glucopyranosyl-(1→6)-3-*O*-decyl-2-deoxy-2-(3-oxotetradecanamido)-α-D-glucopyranose 1-(dihydrogen phosphate)
éritoran	dihydrogénophosphate de 3-*O*-décyl-2-désoxy-6-*O*-[2-désoxy-3-*O*-[(3*R*)-3-méthoxydécyl]-6-*O*-méthyl-2-[(11*Z*)-octadéc-11-énoylamino]-4-*O*-phosphono-β-D-glucopyranosyl]-2-[(3-oxotétradécanoyl)amino]-α-D-glucopyranosyle
eritorán	dihidrógenofosfato de 3-*O*-decil-2-desoxi-6-*O*-[2-desoxi-3-*O*-[(3*R*)-3-metoxidecil]-6-*O*-metil-2-[(11*Z*)-octadec-11-enamido]-4-*O*-fosfono-β-D-glucopiranosil]-2-(3-oxotetradecanamido)-α-D-glucopiranosilo

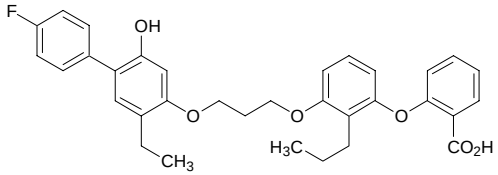
$C_{66}H_{126}N_2O_{19}P_2$



etalocibum

etalocib	2-(3-{3-[(5-ethyl-4'-fluoro-2-hydroxy-[1,1'-biphenyl]-4-yl)oxy]propoxy}-2-propylphenoxy)benzoic acid
étalocib	acide 2-[3-[3-[(5-éthyl-4'-fluoro-2-hydroxybiphényl-4-yl)oxy]propoxy]-2-propylphénoxy]benzoïque
etalocib	ácido 2-[3-[3-[(5-etil-4'-fluoro-2-hidroxibifenil-4-il)oxi]propoxi]-2-propilfenoxi]benzoico

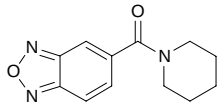
$C_{33}H_{33}FO_6$



farampatorum

farampator	5-[(piperidin-1-yl)carbonyl]-2,1,3-benzooxadiazole
farampator	1-(2,1,3-benzoxadiazol-5-ylcarbonyl)pipéridine
farampator	1-(2,1,3-benzoxadiazol-5-ilcarbonil)piperidina

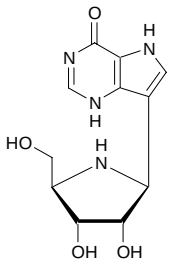
$C_{12}H_{13}N_3O_2$



forodesinum

forodesine	7-(5-amino-1,5-dideoxy-β-D-ribofuranos-1-yl)-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one
forodésine	(-)-7-[(2*S*,3*S*,4*R*,5*R*)-3,4-dihydroxy-5-(hydroxyméthyl)pyrrolidin-2-yl]-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one
forodesina	(-)-7-[(2*S*,3*S*,4*R*,5*R*)-3,4-dihidroxi-5-(hidroximetil)pirrolidin-2-il]-1,5-dihidro-4*H*-pirrolo[3,2-*d*]pirimidin-4-ona

$C_{11}H_{14}N_4O_4$



galsulfasum

galsulfase	*N*-acetylgalactosamine 4-sulfatase (human CSL4S-342 cell)
galsulfase	*N*-acétylgalactosamine 4-sulfatase (cellule humaine CSL4S-342)
galsulfasa	*N*-acetilgalactosamina 4-sulfatasa (célula humana CSL4S-342)

$C_{2529}H_{3843}N_{689}O_{716}S_{16}$

AGASRPPHLV FLLADDLGWN DVGFHGSRIR TPHLDALAAG
GVLLDNYYTQ PLCTPSRSQL LTGRYQIRTG LQHQIIWPCQ
PSCVPLDEKL LPQLLKEAGY TTHMVGKWHL GMYRKECLPT
RRGFDTYFGY LLGSEDYYSH ERCTLIDALN VTRCALDFRD
GEEVATGYKN MYSTNIFTKR AIALITNHPP EKPLFLYLAL
QSVHEPLQVP EEYLKPYDFI QDKNRHHYAG MVSLMDEAVG
NVTAALKSSG LWNNTVFIFS TDNGGQTLAG GNNWPLRGRK
WSLWEGGVRG VGFVASPLLK QKGVKNRELI HISDWLPTLV
KLARGHTNGT KPLDGFDVWK TISEGSPSPR IELLHNIDPN
FVDSSPCPRN SMAPAKDDSS LPEYSAFNTS VHAAIRHGNW
KLLTGYPGCG YWFPPPSQYN VSEIPSSDPP TKTLWLFDID
RDPEERHDLS REYPHIVTKL LSRLQFYHKH SVPVYFPAQD
PRCDPKATGV WGPWM

glucarpidasum

glucarpidase	recombinant glutamate carboxypeptidase (carboxypeptidase G_2)
glucarpidase	[405-arginine]précurseur de la carboxypeptidase G2 de *Pseudomonas* (RS-16), enzyme à zinc dimérique, glutamate carboxypeptidase
glucarpidasa	glutamato carboxipeptidasa recombinante (carboxipeptidasa G2)

$C_{1950}H_{3157}N_{543}O_{599}S_7$ (monomer)

MRPSIHRTAI AAVLATAFVA GTALAQKRDN VLFQAATDEQ
PAVIKTLEKL VNIETGTGDA EGIAAAGNFL EAELKNLGFT
VTRSKSAGLV VGDNIVGKIK GRGGKNLLLM SHMDTVYLKG
ILAKAPFRVE GDKAYGPGIA DDKGGNAVIL HTLKLLKEYG
VRDYGTITVL FNTDEEKGSF GSRDLIQEEA KLADYVLSFE
PTSAGDEKLS LGTSGIAYVQ VNITGKASHA GAAPELGVNA
LVEASDLVLR TMNIDDKAKN LRFNWTIAKA GNVSNIIPAS
ATLNADVRYA RNEDFDAAMK TLEERAQQKK LPEADVKVIV
TRGRPAFNAG EGGKKLVDKA VAYYKEAGGT LGVEERTGGG
TDAAYAALSG KPVIESLGLP GFGYHSDKAE YVDISAIPRR
LYMARRLIMD LGAGK

iboctadekinum

iboctadekin — a recombinant human interleukin-18 with 157 amino acids

iboctadékine — interleukine-18 humaine recombinante (157 aminoacides)

iboctadekina — interleukina-18 humana recombinante (157 aminoácidos)

$C_{801}H_{1264}N_{212}O_{252}S_{10}$

YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDCRD
NAPRTIFIIS MYKDSQPRGM AVTISVKCEK ISTLSCENKI
ISFKEMNPPD NIKDTKSDII FFQRSVPGHD NKMQFESSSY
EGYFLACEKE RDLFKLILKK EDELGDRSIM FTVQNED

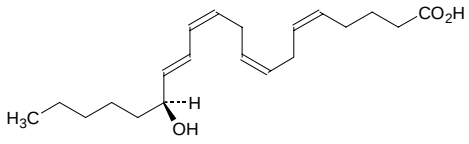
icomucretum

icomucret — (5*Z*,8*Z*,11*Z*,13*E*,15*S*)-15-hydroxyicosa-5,8,11,13-tetraenoic acid

icomucret — acide (5*Z*,8*Z*,11*Z*,13*E*,15*S*)-15-hydroxyicosa-5,8,11,13-tétraénoïque

icomucret — ácido (5*Z*,8*Z*,11*Z*,13*E*,15*S*)-15-hidroxiicosa-5,8,11,13-tetraenoico

$C_{20}H_{32}O_3$



inotuzumabum ozogamicinum

inotuzumab ozogamicin

immunoglobulin G4, anti-(human CD22 (antigen)) (human-mouse monoclonal G544 heavy chain), disulfide with human-mouse monoclonal G544 κ-chain, dimer, conjugate with methyl *N*-{(1*R*,4*Z*,8*S*,13*E*)-8-(4,6-dideoxy-4-{[(4-*S*-{4-[(6-deoxy-3-*O*-methyl-α-L-mannopyranosyl)oxy]-3-iodo-5,6-dimethoxy-2-methylbenzoyl}-4-thio-β-D-*ribo*-hexopyranosyl)oxy]amino}-2-*O*-[4-(*N*-ethylacetamido)-2,4-dideoxy-3-*O*-methyl-α-L-*threo*-pentopyranosyl]-β-D-glucopyranosyloxy)-13-[2-({4-[2-(1-{[4-(4-amino-4-oxobutyl)oxy]phenyl}ethylidene)hydrazinyl]-2-methyl-4-oxobutan-2-yl}disulfanyl)ethylidene]-1-hydroxy-11-oxobicyclo[7.3.1]trideca-4,9-diene-2,6-diyn-10-yl}carbamate

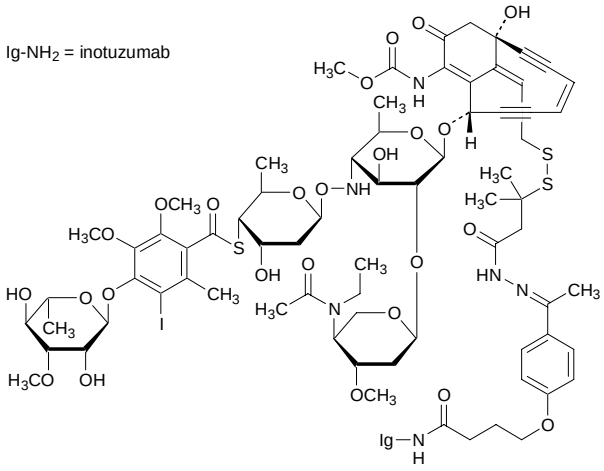
inotuzumab ozogamicine

N-[4-[4-[1-[[3-[[2-[(1*R*,4*Z*,8*S*,13*E*)-8-[[2-*O*-[4-(acétyléthylamino)-2,4-didésoxy-3-*O*-méthyl-α-L-*thréo*-pentopyranosyl]-4,6-didésoxy-4-[[[2,6-didésoxy-4-*S*-[4-[(6-désoxy-3-*O*-méthyl-α-L-mannopyranosyl)oxy]-3-iodo-5,6-diméthoxy-2-méthylbenzoyl]-4-thio-β-D-*ribo*-hexopyranosyl]oxy]amino]-β-D-glucopyranosyl]oxy]-1-hydroxy-10-[(méthoxycarbonyl)amino]-11-oxobicyclo[7.3.1]tridéca-4,9-diène-2,6-diyn-13-ylidène]éthyl]disulfanyl]-3-méthylbutanoyl]=diazanylidène]éthyl]phénoxy]butanoyl]immunoglobuline G4, anti-(antigène CD22 humain) dimère du disulfure entre la chaîne lourde et la chaîne κ de l'anticorps monoclonal de souris G544 humanisé

inotuzumab ozogamicina

N-[4-[4-[1-[[3-[[2-[(1R,4Z,8S,13E)-8-[[2-O-[4-(acetiletilamino)-2,4-didesoxi-3-O-metil-α-L-treo-pentopiranosil]-4,6-didesoxi-4-[[[2,6-didesoxi-4-S-[4-[(6-desoxi-3-O-metil-α-L-manopiranosil)oxi]-3-iodo-5,6-dimetoxi-2-metilbenzoil]-4-tio-β-D-ribo-hexopiranosil]=oxi]amino]-β-D-glucopiranosil]oxi]-1-hidroxi-10-[(metoxicarbonil)=amino]-11-oxobiciclo[7.3.1]trideca-4,9-dieno-2,6-diino-13-ilideno]etil]disulfanil]-3-metilbutanoil]diazanilideno]etil]fenoxi]=butanoil]inmunoglobulina G4, anti-(antigeno CD22 humano) dimero del disulfuro entre la cadena pesada y la cadena κ del anticuerpo monoclonal humanizado de ratón G544

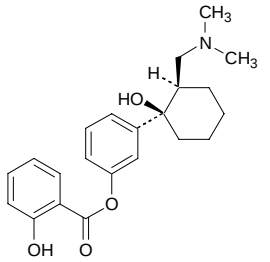
$C_{6518}H_{10002}N_{1738}O_{2036}S_{42}$



isalmadolum

isalmadol	3-{(1*RS*,2*RS*)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl}phenyl 2-hydroxybenzoate
isalmadol	2-hydroxybenzoate de 3-[(1*RS*,2*RS*)-2-[(diméthylamino)méthyl]-1-hydroxycyclohexyl]phényle
isalmadol	2-hidroxibenzoato de 3-[(1RS,2RS)-2-[(dimetilamino)metil]-1-hidroxiciclohexil]fenilo

$C_{22}H_{27}NO_4$

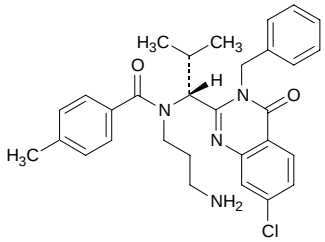


and enantiomer
et énantiomère
y enantiómero

ispinesibum

ispinesib	*N*-(3-aminopropyl)-*N*-[(1*R*)-1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylpropyl]-4-methylbenzamide
ispinésib	*N*-(3-aminopropyl)-*N*-[(1*R*)-1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-méthylpropyl]-4-méthylbenzamide
ispinesib	*N*-(3-aminopropil)-*N*-[(1*R*)-1-(3-bencil-7-cloro-4-oxo-3,4-dihidroquinazolin-2-il)-2-metilpropil]-4-metilbenzamida

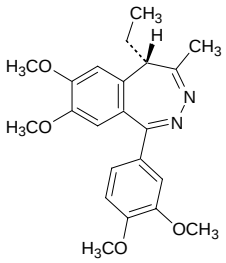
$C_{30}H_{33}ClN_4O_2$



levotofisopamum

levotofisopam	(5*S*)-1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5*H*-2,3-benzodiaxepine
lévotofisopam	(-)-(5*S*)-1-(3,4-diméthoxyphényl)-5-éthyl-7,8-diméthoxy-4-méthyl-5*H*-2,3-benzodiazépine
levotofisopam	(-)-(5*S*)-1-(3,4-dimetoxifenil)-5-etil-7,8-dimetoxi-4-metil-5*H*-2,3-benzodiazepina

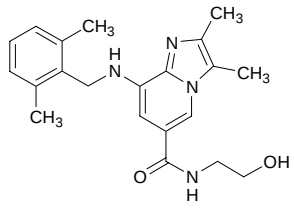
$C_{22}H_{26}N_2O_4$



linaprazanum

linaprazan	8-{[(2,6-dimethylphenyl)methyl]amino}-*N*-(2-hydroxyethyl)-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxamide
linaprazan	8-[(2,6-diméthylbenzyl)amino]-*N*-(2-hydroxyéthyl)-2,3-diméthylimidazo[1,2-*a*]pyridine-6-carboxamide
linaprazán	8-[(2,6-dimetilbencil)amino]-N-(2-hidroxietil)-2,3-dimetilimidazo=[1,2-a]piridina-6-carboxamida

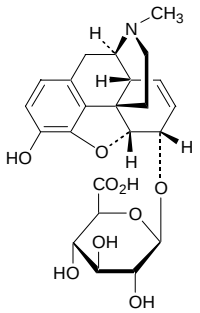
$C_{21}H_{26}N_4O_2$



morphini glucuronidum

morphine glucuronide	3-hydroxy-17-methyl-4,5α-epoxymorphin-7-en-6α-yl β-D-glucopyranosiduronic acid
glucuronide de morphine	acide β-D-glucopyranosiduronique de 7,8-didéshydro-4,5α-époxy-3-hydroxy-17-méthylmorphinan-6α-yle
glucurónido de morfina	ácido β-D-glucopiranosidurónico de 7,8-dideshidro-4,5α-epoxi-3-hidroxi-17-metilmorfinan-6α-ilo

$C_{23}H_{27}NO_9$



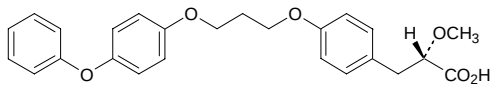
naveglitazarum

naveglitazar — (2*S*)-2-methoxy-3-{4-[3-(4-phenoxyphenoxy)propoxy]phenyl}= propanoic acid

navéglitazar — acide (2*S*)-2-méthoxy-3-[4-[3-(4-phénoxyphénoxy)propoxy]phényl]= propanoïque

naveglitazar — ácido (2*S*)-2-metoxi-3-[4-[3-(4-fenoxifenoxi)propoxi]fenil]propanoico

$C_{25}H_{26}O_6$



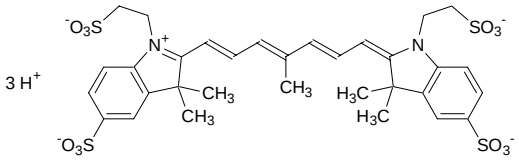
omocianinum

omocianine — 2-{(1*E*,3*E*,5*E*)-7-[(2*E*)-3,3-dimethyl-5-sulfonato-1-(2-sulfonatoethyl)-1,3-dihydro-2*H*-indol-2-ylidene]-4-methylhepta-1,3,5-trienyl}-3,3-dimethyl-1-(2-sulfonatoethyl)-3*H*-indolium-5-sulfonate

omocianine — trihydrogéno-2-[(1*E*,3*E*,5*E*)-7-[(2*E*)-3,3-diméthyl-5-sulfonato-1-(2-sulfonatoéthyl)-1,3-dihydro-2*H*-indol-2-ylidène]-4-méthylhepta-1,3,5-triényl]-3,3-diméthyl-1-(2-sulfonatoéthyl)-3*H*-indolium-5-sulfonate

omocianina — trihidrógeno-2-[(1*E*,3*E*,5*E*)-7-[(2E)-3,3-dimetil-5-sulfonato-1-(2-sulfonatoetil)-1,3-dihidro-2*H*-indol-2-ilideno]-4-metilhepta-1,3,5-trienil]-3,3-dimetil-1-(2-sulfonatoetil)-3*H*-indolio-5-sulfonato

$C_{32}H_{38}N_2O_{12}S_4$



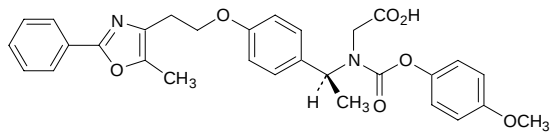
peliglitazarum

peliglitazar — *N*-[(4-methoxyphenoxy)carbonyl]-*N*-[(1*S*)-1-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl}ethyl]glycine

péliglitazar — acide [[(4-méthoxyphénoxy)carbonyl][(1*S*)-1-[4-[2-(5-méthyl-2-phényloxazol-4-yl)éthoxy]phényl]éthyl]amino]acétique

peliglitazar — ácido [[(4-metoxifenoxi)carbonil][(1*S*)-1-[4-[2-(5-metil-2-feniloxazol-4-il)etoxi]fenil]etil]amino]acético

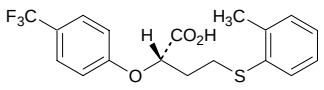
$C_{30}H_{30}N_2O_7$



pemaglitazarum

pemaglitazar	(2*S*)-4-[(2-methylphenyl)sulfanyl]-2-[4-(triflurometh‌yl)phenoxy]= butanoic acid
pémaglitazar	(-)-acide (2*S*)-4-[(2-méthylphényl)sulfanyl]-2-[4-(trifluorométhyl)= phénoxy]butanoïque
pemaglitazar	(-)-ácido (2*S*)-4-[(2-metilfenil)sulfanil]-2-[4-(trifluorometil)fenoxi]= butanoico

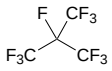
$C_{18}H_{17}F_3O_3S$



perflisobutanum

perflisobutane	1,1,1,2,3,3,3-heptafluoro-2-(trifluoromethyl)propane
perflisobutane	1,1,1,2,3,3,3-heptafluoro-2-(trifluorométhyl)propane
perflisobutano	1,1,1,2,3,3,3-heptafluoro-2-(trifluorometil)propano

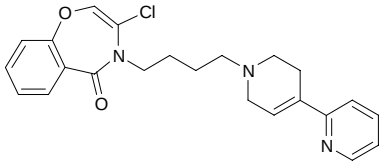
C_4F_{10}



piclozotanum

piclozotan	3-chloro-4-[4-(1',2',3',6'-tetrahydro-[2,4'-bipyridin]-1'-yl)butyl]-1,4-benzoxazepin-5(4*H*)-one
piclozotan	3-chloro-4-[4-(3',6'-dihydro-2,4'-bipyridinyl-1'(2'*H*)-yl)butyl]-1,4-benzoxazépin-5(4*H*)-one
piclozotán	3-cloro-4-[4-(3',6'-dihidro-2,4'-bipiridinil-1'(2'*H*)-il)butil]-1,4-benzoxazepin-5(4*H*)-ona

$C_{23}H_{24}ClN_3O_2$



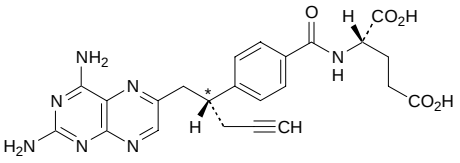
pralatrexatum

pralatrexate — *N*-{4-[1-(2,4-diaminopteridin-6-yl)pent-4-yn-2-yl]benzoyl}-L-glutamic acid

pralatrexate — acide (2*S*)-2-[[4-[(1*RS*)-1-[(2,4-diaminoptéridin-6-yl)méthyl]but-3-ynyl]benzoyl]amino]pentanedioïque

pralatrexato — ácido (2S)-2-[[4-[(1RS)-1-[(2,4-diaminopteridin-6-il)metil]but-3-inil]benzoil]amino]pentanodioico

$C_{23}H_{23}N_7O_5$



and epimer at C*
et l'épimère en C*
y el epímero en C*

radoterminum

radotermin — growth differentiation factor 5 (human), homodimer

radotermine — facteur 5 humain de différenciation de la croissance, homodimère produit par *E. coli*

radotermina — factor 5 humano de diferenciación del crecimiento homodímero producido por *E. coli*

$C_{1184}H_{1844}N_{330}O_{350}S_{22}$

raxibacumabum

raxibacumab — immunoglobulin G1, anti-(anthrax protective antigen) (human monoclonal PA heavy chain), disulfide with human monoclonal PA λ-chain, dimer

raxibacumab — immunoglobuline G1, anti-(antigen protecteur de l'anthrax), dimère du disulfure entre la chaine lourde et la chaîne λ de l'anticorps monoclonal humain PA

raxibacumab — inmunoglobulina G1, anti-(antígeno protector del antrax), dímero del disulfuro entre la cadena pesada y la cadena λ del anticuerpo monoclonal humano PA

$C_{6320}H_{9794}N_{1702}O_{1998}S_{42}$

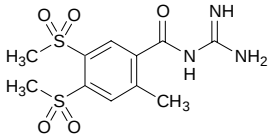
rimeporidum

rimeporide — *N*-(aminoiminomethyl)-4,5-bis(methanesulfonyl)-2-methylbenzamide

riméporide — *N*-carbamimidoyl-2-méthyl-4,5-bis(méthylsulfonyl)benzamide

rimeporida — *N*-carbamimidoil-2-metil-4,5-bis(metilsulfonil)benzamida

$C_{11}H_{15}N_3O_5S_2$



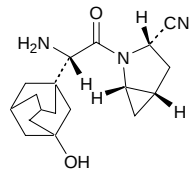
saxagliptinum

saxagliptin — (1*S*,3*S*,5*S*)-2-{(2*S*)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl}-2-azabicyclo[3.1.0]hexane-3-carbonitrile

saxagliptine — (1*S*,3*S*,5*S*)-2-[(2*S*)-amino(3-hydroxytricyclo[3.3.1.1^{3,7}]déc-1-yl)=acétyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile

saxagliptina — (1*S*,3*S*,5*S*)-2-[(2*S*)-amino(3-hidroxitriciclo[3.3.1.1^{3,7}]dec-1-il)acetil]-2-azabiciclo[3.1.0]hexano-3-carbonitrilo

$C_{18}H_{25}N_3O_2$



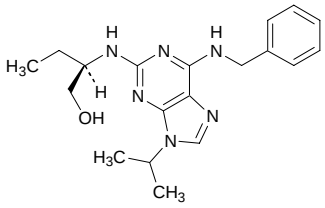
seliciclibum

seliciclib — (2*R*)-2-{[6-benzylamino-9-(propan-2-yl)-9*H*-purin-2-yl]amino}butan-1-ol

séliciclib — (-)-(2*R*)-2-[[6-(benzylamino)-9-(1-méthyléthyl)-9*H*-purin-2-yl]amino]=butan-1-ol

seliciclib — (-)-(2*R*)-2-[[6-(bencilamino)-9-(1-metiletil)-9*H*-purin-2-il]amino]butan-1-ol

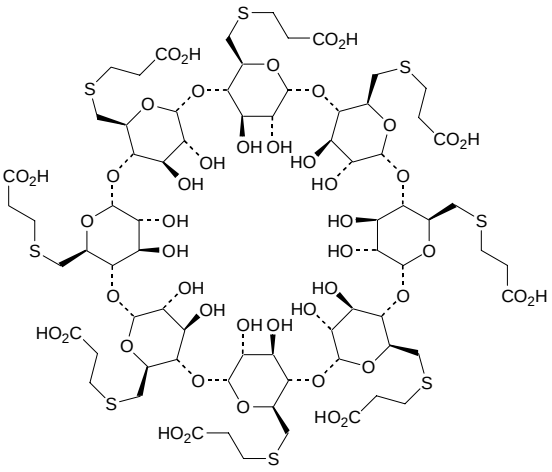
$C_{19}H_{26}N_6O$



sugammadexum

sugammadex	cyclooctakis-(1→4)-[6-*S*-(2-carboxyethyl)-6-thio-α-D-glucopyranosyl]
sugammadex	cyclooctakis-(1→4)-[6-*S*-(2-carboxyéthyl)-6-thio-α-D-glucopyranosyl]
sugammadex	ciclooctakis-(1→4)-[6-S-(2-carboxietil)-6-tio-α-D-glucopiranosil]

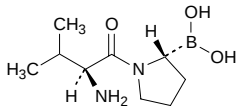
$C_{72}H_{112}O_{48}S_8$



talabostatum

talabostat	{(2*R*)-1-[(2*S*)-2-amino-3-methylbutanoyl]pyrrolidin-2-yl}boronic acid
talabostat	acide [(2*R*)-1-[(2*S*)-2-amino-3-méthylbutanoyl]pyrrolidin-2-yl]= boronique
talabostat	ácido [(2*R*)-1-[(2*S*)-2-amino-3-metilbutanoil]pirrolidin-2-il]borónico

$C_9H_{19}BN_2O_3$



talactoferrinum alfa

talactoferrin alfa	lactoferrin (recombinant human LF00)
talactoferrine alfa	[11-L-thréonine,29-L-arginine]lactotransferrine humaine produite par *Aspergillus niger* var. *awamori*
talactoferrina alfa	[11-L-treonina,29-L-arginina]lactotransferrina humana producida por *Aspergillus niger* var. *awamori*

$C_{3345}H_{5215}N_{963}O_{1015}S_{37}$ (peptide)

GRRRRSVQWC TVSQPEATKC FQWQRNMRRV RGPPVSCIKR
DSPIQCIQAI AENRADAVTL DGGFIYEAGL APYKLRPVAA
EVYGTERQPR THYYAVAVVK KGGSFQLNEL QGLKSCHTGL
RRTAGWNVPI GTLRPFLNWT GPPEPIEAAV ARFFSASCVP
GADKGQFPNL CRLCAGTGEN KCAFSSQEPY FSYSGAFKCL
RDGAGDVAFI RESTVFEDLS DEAERDEYEL LCPDNTRKPV
DKFKDCHLAR VPSHAVVARS VNGKEDAIWN LLRQAQEKFG
KDKSPKFQLF GSPSGQKDLL FKDSAIGFSR VPPRIDSGLY
LGSGYFTAIQ NLRKSEEEVA ARRARVVWCA VGEQELRKCN
QWSGLSEGSV TCSSASTTED CIALVLKGEA DAMSLDGGYV
YTAGKCGLVP VLAENYKSQQ SSDPDPNCVD RPVEGYLAVA
VVRRSDTSLT WNSVKGKKSC HTAVDRTAGW NIPMGLLFNQ
TGSCKFDEYF SQSCAPGSDP RSNLCALCIG DEQGENKCVP
NSNERYYGYT GAFRCLAENA GDVAFVKDVT VLQNTDGNNN
EAWAKDLKLA DFALLCLDGK RKPVTEARSC HLAMAPNHAV
VSRMDKVERL KQVLLHQQAK FGRNGSDCPD KFCLFQSETK
NLLFNDNTEC LARLHGKTTY EKYLGPQYVA GITNLKKCST
SPLLEACEFL RK

* glycosylation site
* sites de glycosylation
* posición de glicosilación

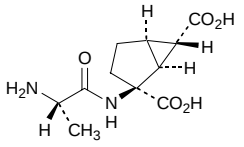
talaglumetadum

talaglumetad — (1*S*,2*S*,5*R*,6*S*)-2-[(2*S*)-2-aminopropanamido]bicyclo[3.1.0]hexane-2,6-dicarboxylic acid

talaglumétad — acide (1*S*,2*S*,5*R*,6*S*)-2-[[(2*S*)-2-aminopropanoyl]amino]=bicyclo[3.1.0]hexane-2,6-dicarboxylique

talaglumetad — ácido (1*S*,2*S*,5*R*,6*S*)-2-[[(2*S*)-2-aminopropanoil]amino]=biciclo[3.1.0]hexano-2,6-dicarboxílico

$C_{11}H_{16}N_2O_5$



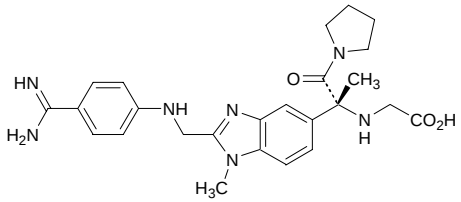
tanogitranum

tanogitran — *N*-[(2*R*)-2-{2-[(4-carbamimidoylanilino)methyl]-1-methyl-1*H*-benzimidazol-5-yl}-1-oxo-1-(pyrrolidin-1-yl)propan-2-yl]glycine

tanogitran — acide [[(1*R*)-1-[2-[[(4-carbamimidoylphényl)amino]méthyl]-1-méthyl-1*H*-benzimidazol-5-yl]-1-méthyl-2-oxo-2-(pyrrolidin-1-yl)éthyl]=amino]acétique

tanogitrán — ácido [[(1*R*)-1-[2-[[(4-carbamimidoilfenil)amino]metil]-1-metil-1*H*-bencimidazol-5-il]-1-metil-2-oxo-2-(pirrolidin-1-il)etil]amino]=acético

$C_{25}H_{31}N_7O_3$



tefibazumabum

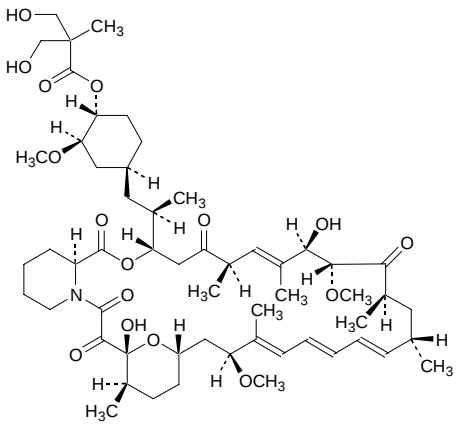
tefibazumab	immunoglobulin G1, anti-(*Staphylococcus aureus* protein ClfA (clumping factor A)) (human-*Mus musculus* monoclonal Aurexis heavy chain), disulfide with human-*Mus musculus* monoclonal Aurexis κ-chain, dimer
téfibazumab	immunoglobuline G1, anti-(protéine ClfA (facteur A d'agrégation) de *Staphylococcus aureus*) dimère du disulfure entre la chaîne lourde et la chaîne κ de l'anticorps monoclonal *Mus-musculus* Aurexis humanisé
tefibazumab	inmunoglobulina G1, anti-(proteína ClfA (factor A de agregación) de *Staphylococcus aureus*) dimero del disulfuro entre la cadena pesada y la cadena κ del anticuerpo monoclonal humano *Mus-musculus* Aurexis

$C_{6548}H_{10122}N_{1730}O_{2034}S_{44}$

temsirolimusum

temsirolimus	(1*R*,2*R*,4*S*)-4-{(2*R*)-2-(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetracosahydro-3*H*-23,27-epoxypyrido[2,1-*c*][1,4]=oxazacyclohentriacontin-3-yl]propyl}-2-methoxycyclohexyl 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate
temsirolimus	3-hydroxy-2-(hydroxyméthyl)-2-méthylpropanoate de (1*R*,2*R*,4*S*)-4-[(2*R*)-2-[(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,27-dihydroxy-10,21-diméthoxy-6,8,12,14,20,26-hexaméthyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tétracosahydro-23,27-époxy-3*H*-pyrido[2,1-*c*][1,4]oxazacyclohentriacontin-3-yl]propyl]-2-méthoxycyclohexyle
temsirolimus	3-hidroxi-2-(hidroximetil)-2-metilpropanoato de (1*R*,2*R*,4*S*)-4-[(2*R*)-2-[(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,27-dihidroxi-10,21-dimetoxi-6,8,12,14,20,26-hexametil-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetracosahidro-23,27-epoxi-3*H*-pirido[2,1-*c*][1,4]oxazaciclohentriacontin-3-il]propil]-2-metoxiciclohexilo

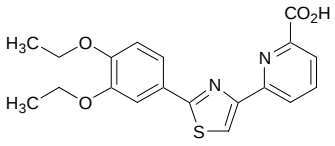
$C_{56}H_{87}NO_{16}$



tetomilastum

tetomilast	6-[2-(3,4-diethoxyphenyl)-1,3-thiazol-4-yl]pyridine-2-carboxylic acid
tétomilast	acide 6-[2-(3,4-diéthoxyphényl)thiazol-4-yl]pyridine-2-carboxylique
tetomilast	ácido 6-[2-(3,4-dietoxifenil)tiazol-4-il]piridina-2-carboxílico

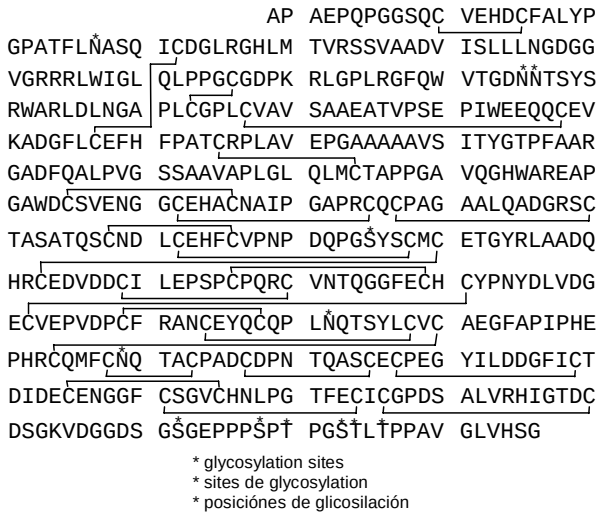
$C_{19}H_{18}N_2O_4S$



thrombomodulinum alfa

thrombomodulin alfa	1-498-thrombomodulin (human clone TMP26/TMJ1 protein moiety reduced)
thrombomoduline alfa	[473-valine]précurseur de la thrombomoduline humaine-(19-516)-peptide (protéine soluble)
trombomodulina alfa	[473-valina]precursor de la trombomodulina humana-(19-516)-péptido (proteína soluble)

$C_{2230}H_{3357}N_{633}O_{718}S_{50}$



* glycosylation sites
* sites de glycosylation
* posiciónes de glicosilación

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

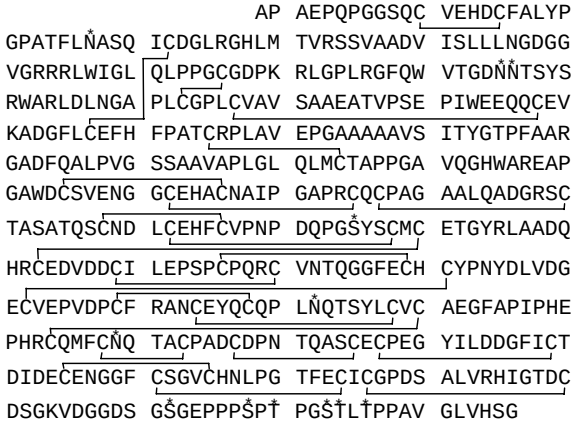
Proposed International Non Proprietary Names (Prop. INN): List 92
Dénominations communes internationales proposées (DCI Prop.): Liste 92
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 92
(WHO Drug Information, Vol. 18, No. 4, 2004)

	suprimáse	*insértese*
p. 351	**temserolimusum**	**temsirolimusum**
	temserolimus	temsirolimus

p. 354 **thrombomodulinum alfa**

thrombomodulin alfa
thrombomoduline alfa
trombomodulina alfa

replace the graphic formula by the following:
remplacer la formule développée par:
sustitúyase la fórmula desarrollada por:



* glycosylation sites
* sites de glycosylation
* posiciónes de glicosilación

Recommended International Nonproprietary Names (Rec. INN): List 16
Dénominations communes internationales recommandées (DCI Rec.): Liste 16
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 16
(WHO Drug Information, Vol. 30, No. 10, 1976)

p. 6 **nosiheptidum**

nosiheptide
nosiheptide
nosiheptida

replace the molecular formula by the following:
remplacer la formule brute par:
sustitúyase la fórmula empírica por:

$C_{51}H_{43}N_{13}O_{12}S_6$

Recommended International Nonproprietary Names (Rec. INN): List 34
Dénominations communes internationales recommandées (DCI Rec.): Liste 34
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 34
(WHO Drug Information, Vol. 8, No. 3, 1994)

	suprimase	*insértese*
p. 5	bosentano	bosentán

Recommended International Nonproprietary Names (Rec. INN): List 52
Dénominations communes internationales recommandées (DCI Rec.): Liste 52
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 52
(WHO Drug Information, Vol. 18, No. 3, 2004)

p. 252	*suprimáse* esoxybutynina	*insértese* esoxibutinina
p. 258	*suprimáse* ramelteòn	*insértese* ramelteón

Recommended International Nonproprietary Names (Rec. INN): List 53
Dénominations communes internationales recommandées (DCI Rec.): Liste 53
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 53
(WHO Drug Information, Vol. 19, No. 1, 2005)

p. 74 **dasantafilum**

dasantafil — *replace the chemical name by the following:*

7-(3-bromo-4-methoxyphenylmethyl)-1-ethyl-8-{[(1*R*,2*R*)-2-hydroxycyclopentyl]=amino}-3-(2-hydroxyethyl)-3,7-dihydro-1*H*-purine-2,6-dione

p. 75 **deluceminum**

delucemine — *replace the molecular formula by the following:*
délucémine — *remplacer la formule brute par:*
delucemina — *sustitúyase la fórmula empírica por:*

$C_{16}H_{17}F_2N$

p. 84 **maravirocum**

maraviroc — *replace the chemical name by the following:*

4,4-difluoro-*N*-[(1*S*)-3-{(1*R*,3*s*,5*S*)-3-[3-methyl-5-(propan-2-yl)-4*H*-1,2,4-triazol-4-yl]-8-azabicyclo[3.2.1]octan-8-yl}-1-phenylpropyl]cyclohexanecarboxamide

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 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 listes des DCI 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 las listas de DCI propuestas.