PROPOSED INN LIST 82
INTERNATIONAL NONPROPRIETARY NAMES
FOR PHARMACEUTICAL SUBSTANCES

WORLD HEALTH ORGANIZATION • GENEVA
General Policy Issues

Access to essential drugs
A conference on Increasing Access to Essential Drugs in a Globalized Economy: Working Towards Solutions was organized by Médecins Sans Frontières, Health Action International, and Consumer Project on Technology in Amsterdam, the Netherlands, on November 25–26, 1999.

Access to essential drugs is of importance to the World Health Organization whose longstanding aim is to ensure equity of access and rational use of essential drugs of quality. This underpins the fundamental right to health care by all people. WHO has made tangible progress towards securing this right but there is still a long way to go. As a result of the conference, a statement was prepared for presentation to the World Trade Organization (WTO) during their subsequent conference in Seattle calling on Member States to consider the needs of developing countries by strengthening TRIPS provisions with regard to public health priorities.

WHO’s role in ensuring access to essential drugs
Dr Michael Scholtz, Executive Director, Health Technology and Pharmaceuticals, World Health Organization

It is agreed that essential drugs save lives and improve health yet there are millions of people who lack regular access to essential medicines. Three factors are critical in securing access: sustainable financing, affordable prices, and reliable supply systems. Additionally, drugs must be rationally selected, appropriately used, and of assured quality.

Sustainable financing
Payment for essential drugs through general government revenues and social health insurance is the preferred approach to financing. Such an approach has achieved the greatest equity and solidarity and is the best long-term investment in health.

The evidence is clear. Countries that invest wisely in health also experience greater economic development. This means that adequate funding must be allocated for essential drugs and high-impact public health problems targeted. In this, governments must play their role. WHO continues to promote better and increased spending on health and advocates the inclusion of a health component as part of poverty reduction strategies.

One promising trend is the increase in social and private health insurance coverage and expanded public health benefits for rural and low income populations. Since drugs represent 25–70% of total costs for these schemes, WHO’s role is to promote the essential drugs concept. There is also a need to address the particularities of pharmaceutical management within health insurance schemes. User charges and private, out-of-pocket spending on essential drugs should be seen merely as transitional measures to more equitable public financing and social health insurance.

The feasibility of endowment funds and other innovative financing mechanisms for eradication and control of specific communicable diseases in the least developed countries is being studied. Such a sustainable external source of financing may be the only realistic way to contribute to access in the poorest countries.

We have also seen an increasing number of targeted drug and vaccine donation programmes, aimed at specific diseases. In the mid-term we must be able to establish donations as a sustainable part of a drug distribution system. However, in the long-term, only self-sufficiency can be the answer to a real reduction of the disease burden.

Affordable prices
A variety of measures exist to contain pharmaceutical prices paid by governments and the costs paid through health insurance programmes. Many of
these measures can also be used to contain direct consumer expenditure. In developing countries, up to 90% of drugs are paid “out of pocket”, representing the largest household health expenditure in these countries.

Manufacturers’ selling prices can be contained through competition, volume purchasing, and price controls. Competition among therapeutically similar patented drugs can bring down prices. This effect is beginning to be seen even among HIV drugs. But measures to reduce manufacturers’ prices can only be part of the strategy. While in developed countries, manufacturers’ prices typically represent 50–60% of the final consumer price, in developing countries the manufacturers’ selling price can be as little as 20% of that finally paid by the consumer with up to 80% of the price consisting of import duties, taxes, distribution costs, and dispensing fees.

WHO supports the reduction or even elimination of import duties for pharmaceuticals. Equally, a reduction of national and local taxes needs to be negotiated and reasonable levels of distribution and dispensing mark-ups sought. A number of countries are moving to a system of fixed professional dispensing fees which reduces the incentive for the pharmacist or drug seller to dispense higher cost products. Price information for health professionals and consumers is essential for making an informed choice.

Reliable supply systems
The third critical element for access to essential drugs is a reliable mix of public and private sector supply systems. Many countries continue to struggle with an unfortunate combination of inefficient public systems meant to serve the entire country alongside private supply systems serving urban areas. Decentralization of public services sometimes compounds the problem. Yet we have seen progress through innovative approaches to public and private supply systems in many countries. These promising developments have much to teach us.

In summary, addressing the problem of access to essential drugs will depend on dealing with all three critical factors. Too often, manufacturers who should be working to reduce prices are busy blaming unreliable supply systems; policy-makers in a position to influence drug financing are busy blaming high prices; and health care managers who could improve supply systems are busy blaming inadequate financing. Instead, all parties should work toward a common solution.

Multilateral trade agreements and access to essential drugs
With the establishment of the World Trade Organization (WTO) in 1995, several new treaties came into force which are binding on all WTO members. Among these agreements, TRIPS (Trade-Related Aspects of Intellectual Property Rights) has been of greatest significance with respect to pharmaceuticals. Previously, countries adopted various approaches to drug patents suited to individual policies and needs.

Intellectual property laws affecting pharmaceuticals cannot be viewed separately from the health systems in which they operate. Thus it is not the TRIPS agreement which is to be blamed for the failure to provide access to essential drugs; neither is it the existence of the multilateral TRIPS agreement on intellectual property that is under discussion. It is the implementation of TRIPS provisions and the impact of their mid-term and long-term effects.

WHO has identified the following public health implications of patent protection related to pharmaceuticals.

1. Patent protection stimulates research and development
Patent protection is a necessary and effective incentive for research and development for needed new pharmaceuticals. Intellectual property laws specify the rights of the patent holder and the public and ensure benefits for both parties. However, pharmaceuticals cannot be regarded simply as commodities. Thus, WHO supports countries in using the safeguards provided in TRIPS, as needed, to ensure equitable access to drugs. These safeguards include extension of the transition period, disclosure of inventions, compulsory licensing and exceptions to support the marketing of generic drugs.

2. Priority setting for R&D neglects many endemic diseases
As the balance between demand and supply for pharmaceuticals is often imperfect, so is the priority-setting for investing in related research and development (R&D). Although patents have stimulated the discovery of new drugs, it does not follow that these new drugs are affordable to all people or that they have met the most pressing therapeutic...
needs. Increasing concern is expressed that research and development in the pharmaceutical industry follows industrialized countries’ market demands. Tropical diseases, endemic in countries where little money is available for drugs, are particularly neglected.

Therefore, WHO is working with public and private sector partners to create mechanisms and incentives that drive research and development into areas of high medical need, especially where there is a high burden of disease in lower income countries. The recently created “Medicines for Malaria Venture” and the “Global Alliance for Vaccines and Immunization” are concrete initiatives addressing this concern. Such innovations and patents created with public funds should, as a rule, be licensed on a non-exclusive basis in order to encourage competition, at least for those products applicable to diseases that are at the centre of public health concern.

3. Preferential pricing is essential for lower-income countries and must be actively pursued Lower-income countries are simply unable to pay the same prices for essential drugs as the wealthier countries. WHO strongly supports efforts to develop mechanisms for preferential prices for essential drugs in lower-income countries. For governments, industry and other interested parties there is a range of options which might be used to achieve more equitable pricing. These include voluntary licensing with technology transfer and market segmentation through lower cost presentations. At the same time, where lower income countries are benefiting from preferential prices, export of preferentially priced goods into high income markets must be prevented.

4. Generic competition should begin promptly at patent expiry WHO has long promoted public sector use of generic drugs which are subject to the same standards of quality, safety and efficacy as innovator products. WHO is in favour of “early workings” of patented drugs by generic manufacturers to encourage competition as a way of improving these products and providing early access to generic essential drugs. Experience in countries with “generic-friendly” policies demonstrate that the resulting market competition greatly increases affordability of drugs for the population, stimulates genuine innovation within the research-based industry, and encourages higher standards and greater efficiency by the generic industry and local production of essential drugs.

5. Health regulations should not become unwarranted barriers to trade
The objective of the WTO Agreement on Technical Barriers to Trade (TBT) is to ensure that unnecessary obstacles to international trade are not created. Within this agreement, technical regulations and procedures should be based on scientifically developed, international standards, guidelines and recommendations. In the area of pharmaceuticals, WHO norms, standards, and guidelines represent international consensus.

In addition, there are a number of regional and cross-regional efforts aimed at harmonization of regulatory requirements. These efforts are instructive and often achieve technologically demanding standards. It is important, however, that such initiatives involving smaller groupings of countries should be developed in a manner which serves the interests of public health, rather than trade interests. To the contrary, such harmonization initiatives will build trade fortresses and disfavour equitable access to drugs.

WHO’s broader role with respect to international trade agreements and public health
A motivating factor behind the WTO agreements was the argument that they would work to the benefit of all. Patent protection would promote research and development of needed new drugs, ensure a vigorous and dynamic pharmaceutical industry, encourage transfer of technology, strengthen pharmaceutical production in developing countries and contribute to enhanced access. Measures provided in other WTO agreements would protect public health and prevent barriers to trade for pharmaceuticals and other health care services.

Because of the potential health effects of international trade agreements, WHO has taken on several broader roles in relation to globalization. First, WHO must ensure that trade liberalization contributes towards a more equitable distribution of economic benefits and a just society. This requires working with governments in an effort to link trade agreements to sound social policies that recognize health as a global public goal. In the pharmaceutical arena there is a need to provide sufficient incentives and patent protection to ensure development of needed new drugs, while ensuring affordability and access both to existing and new essential drugs. This cannot be seen as an either/or situation or as one objective overwhelming another. An important requirement here is to strengthen the position of ministers of health within governments.
when decisions on trade, finance and health issues are in debate.

Second, WHO supports countries when invoking the safeguards in WTO agreements which permit graduated implementation. Historically, industrialized countries have strengthened their patent laws as they have developed. Several developing countries argue that they do not have either the human or financial resources to benefit from TRIPS and fear a negative effect on public health in their countries. WHO is ready to collaborate with Member States considering application of the provisions for extensions of the transition period that are available within the agreement.

Third, WHO is working with countries to monitor the impact of trade agreements on the availability and affordability of health services, including essential drugs. Such monitoring will help to develop a common methodology for evaluating the effects of TRIPS and trade related agreements.

In conclusion, WHO looks forward to continuing and enhancing collaboration in the future and will strive to improve universal, equitable access to essential drugs. Trade and health must go hand in hand if poverty and the disease burden are to be reduced.

Access to medicines: an urgent need for solutions

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There is a multiplicity of dilemmas inherent in the quest for solutions to the problem of access to medicines. Though it might initially be uncomfortable for some, the problem is crying out for some original thought and policy creativity. It is my belief that it is important to contribute to workable solutions when faced with real and seemingly intractable problems such as the present debate on access to medicines. This debate is also intimately linked to the strategic future of the pharmaceutical industry. If that industry ignores the debate — or hides from it — it will be to its own cost and that of the global community. I have attempted to address below some of the issues involved in promoting access to medicines in the developing world and evaluate some of the proposals which have been made so far. Finally, I explore some possible directions which could be taken in the search for real and sustainable solutions.

1. The role of patents and intellectual property rights: is there a problem?

It is argued that the Trade Related Aspects of Intellectual Property Rights (TRIPS) Agreement is at the heart of the problem of access to medicines for people in developing countries and that patents are the root cause of the problem. It is also claimed that relaxing patent law through a TRIPS review will miraculously promote equitable access to health care.

It is difficult to understand why patents are seen as being such a problem. In reality, about ten of the 300 or so medicines on the WHO Model List of Essential Drugs are still under patent and, of these, all but one will be off patent within the next three years. If TRIPS is such a problem, and patents the root — or even sole — cause of the access problem, people in developing countries should today have unlimited and unhindered access to almost all the generic drugs on the WHO Model List.

In practice, patents can be seen as creating a burden-sharing mechanism between rich and poor. Funding for research and development comes from current revenue derived principally from patented products. In reality, institutions and companies in the rich countries of the northern hemisphere carry the burden of paying for pharmaceutical innovation with the USA and Europe paying for probably 80% of innovation. I do not think anyone would seriously want that to change.

2. Compulsory licensing, parallel trade and differential prices

The R&D-based pharmaceutical industry is not opposed to the compulsory licensing provisions within the current TRIPS. TRIPS is a package of measures which have been negotiated and are intended to be balanced and mutually beneficial. I do not think this has been said clearly enough by my industry. It should have been, because the result of not saying it is an increasing chorus of dissatisfaction about the underlying principles of TRIPS. It has also been said by representatives of some nongovernmental organizations that “compulsory licensing is an extreme measure for extreme cases”. We agree!

What is increasingly being proposed now, however, is not compulsory licensing within TRIPS, but the widespread, irresponsible and systematic use of compulsory licensing beyond TRIPS. If we are in the business of developing new medicines, which we all agree are needed, then creating a massive
hole in TRIPS and going further than TRIPS will not help. It runs the risk of deterring research — which is against the interests of all patients, including those in the developing countries. It would probably also have the inverse effect of focusing even more research on diseases of the industrialized world. It is in all our interests — north and south, rich and poor, industry and patient — that compulsory licensing be an option of last resort.

Some propose parallel trade as another solution, arguing that price differences between countries can be exploited to create access. We all agree that price differences between countries exist. In Europe, for example, price differences can generate massive returns for arbitragers in the parallel trade business. But Europe is increasingly a single political entity, and European health care systems are converging. One day, maybe not far away, this will mean similar levels of economic development and very similar, if not single, prices for medicines within Europe. At that point the arbitragers will be out of business.

But care is needed with parallel trade. It has taken 50 years of political integration to get to the point where people in the health care business in Europe — including governments — start to think about single prices in a single market, and even now there are not many that do. So do not fall for the idea that “if parallel trade is OK for Europe — it must be OK elsewhere”. It really is not that simple.

We need to look seriously at why price differences exist. There should be only one answer: to promote access. The whole point of differentiated, tiered, or “steeply preferential” prices is to sell drugs to people and governments who would otherwise not be able to afford them. You do not need to be an expert to see that a global single price would be a disaster for the developing world. Averaged, global prices would lead to even higher prices in the developing countries than now. It might even be the case that parallel trade could promote price convergence and higher than ever prices in poorer countries.

We must also not forget that most governments play a dominant role in health care — and health care is a controversial and highly political area of public policy. The pharmaceutical industry is hardly likely to refuse to supply governments, wherever they are, most of the time. When governments tender, the prices do come down dramatically — and rightly so — in the majority of cases.

3. The real barriers to access: lack of health care infrastructure and global inequality

The access to medicines debate is about a world in which hospitals frequently do not exist, where clinics are a five-hour walk away, and where millions die every year from diseases which are easily treatable. This is a world of child labour, child mortality and child soldiers, of a massive population explosion, and a world where four-fifths of the people do not have access to, or cannot afford, health care.

Even if medicines were given away in this kind of setting many countries would simply not be able to distribute or use them effectively. Some countries just cannot afford the costs that come with providing access to medicines. This points to the real problems of global inequality, social injustice and the distribution of wealth within countries and between hemispheres. It worries me to hear discussions centred on patents or prices or parallel trade or compulsory licensing, and the accompanying demonizing of big business, while the real problem of poverty and everything that sustains it is neglected.

Solutions

During a series of roundtables organized by WHO last year in Geneva (1, 2) a great deal was said about the need for balance and burden-sharing. This, logically, is where we should start. The pharmaceutical industry certainly needs to be more creative about access to health care and the political environment surrounding it. Four points demand immediate attention: donations, research and development agendas, prices, and social responsibility.

1. Donations

There is now a relatively long history of major philanthropic gestures being made by the pharmaceutical industry. I am not a great believer in charity as a mechanism for solving problems which, fundamentally, are caused by socioeconomic and political inequality. But it is undeniable that charity does help. It is an element of burden-sharing which should be welcomed when it happens and expected from industry. A reasonable objective here would be for philanthropy to mature into structured partnerships with humanitarian aid and public health organizations. This could be good because it would lead to balanced relationships based on trust and effective management.
However, the problems should not be underestimated. A major donation programme to eliminate lymphatic filariasis has recently been launched by SmithKline Beecham, WHO, the World Bank and Merck and Co. It has taken us an incredible 18 months to get the first dose of albendazole administered. This indicates the real infrastructural problems we face in the field. These are not limited to problems of poverty but of mobilizing support and organization.

2. Research and development agendas
How do we mobilize research for diseases where markets do not exist? One solution put forward is to promote publicly-funded R&D associated with generic manufacture. If only it were that simple.

In reality, there are basically three ways of encouraging this kind of research and development:

• Global or multinational funding partnerships: the Medicines for Malaria Venture (MMV) is an example of how to identify mechanisms for providing affordable and appropriate antimalarial drugs.

• Research incentives such as extending patent duration on northern hemisphere “blockbuster” drugs to finance research and development aimed at meeting the needs of developing countries.

I like this idea because it provides incentives to do research that otherwise would not be carried out. It also promotes real burden-sharing since we can negotiate the length of patent extension and the number of drugs for tropical diseases to benefit. Unfortunately, the generics manufacturers are likely to oppose this idea because they want their commercial return in Europe and the USA as soon as possible. They might well put this interest above the needs of developing countries.

• Specific mechanisms such as Orphan Drug legislation and accelerated approval processes which could include incentives and various funding possibilities.

3. Prices
It is probable that differentiated prices are part of the solution. Not everyone will agree, but price mechanisms can be seen as one way of creating access to medicines in the developing world. It is also recognized that a standard single global price would undoubtedly lead to higher prices for many developing countries.

It has also been suggested that in exchange for cheap, or sometimes even cost-price medicines, developing country governments might outlaw parallel trade from their countries. This is an interesting idea worth serious study. It could herald a realistic deal which will lead to tangible progress. It would be a real “exception sanitaire” from TRIPS! And it would be a win-win solution for both public health and the R&D industry. Not only would such an idea promote access to medicines today, but it would also encourage the kind of business transformation beyond the USA and Europe which the pharmaceutical industry needs to maintain its future.

4. Social responsibility
Finally, we must not forget the investment community. Political change is about influencing the context in which decisions are made just as much as it is about influencing the decisions themselves. There is lots of evidence that the investment community is slowly increasing its social responsibility. Evidence indicates that it might well make good commercial sense for industry to be just a little more aware and responsive to the socioeconomic conditions and needs of underprivileged populations of the world.

The choice
I think we have a choice between realistic policy options which confront the effects of global inequality and poverty, and those which are outwardly attractive and simplistic but which could actually be counter-productive. Realistic options would be to:

• transform donation programmes into structured partnerships rather than charitable operations;

• implement legislation which positively influences R&D agendas and funding;

• endorse differentiated and fair prices; and

• create a more equitable and sustainable future for tomorrow’s global community while maintaining a healthy R&D industry.

These kind of options will keep the pharmaceutical business motivated and innovative. We need to keep new medicines coming through the pipeline. This risks not happening through tinkering with TRIPS. To focus on opening up TRIPS, or putting massive holes in it, runs the risk of delaying real action on access to medicines for five to ten years, if not indefinitely. That would seem to me too great a risk to take.
Amsterdam statement on access to medicines*

In the developing world, a lucrative or “viable” market for lifesaving drugs simply does not exist. But clearly what does exist is need. The market has failed both to provide equitably priced medicines and to ensure research and development for infectious diseases. This lack of affordable medicines, and research and development for neglected diseases is causing avoidable human suffering. Market forces alone will not address this need: political action is demanded.

At the Amsterdam conference, participants called for health to be made a priority at the WTO Seattle negotiations and demanded a balance between the rights of patent holders and the rights of citizens in intellectual property rights regulations. These views were shared by representatives of UNDP, the WHO, the WTO, members of the Governments of the Netherlands and Thailand, as well as non-governmental organizations attending the Amsterdam conference. The meeting brought together 350 participants from 50 developing and developed countries, from the private and public sectors.

Organizers of the Amsterdam meeting call for the WTO to create a Standing Working Group on Access to Medicines. This working group would work with the Council for TRIPS and other WTO bodies to review a number of issues concerning intellectual property rules, as they relate to access to medicines. The Standing Working Group on Access to Medicines should work within the WTO to consider the impact of trade policies on people in developing and least developed countries, and provide a public health framework for the interpretation of key features of WTO agreements. The WHO and other relevant international organizations should play an active role to support the activities of the working group. The TRIPS Agreement is meant to protect intellectual property rights while also protecting and advancing various public interest objectives. This balance must be addressed to ensure that people have access to essential and life-saving medicines.

As countries implement the TRIPS agreements, the WTO will be asked to resolve disputes in areas that are subject to numerous different interpretations. The WTO is also constantly evaluating proposals for changing the TRIPS Agreement. The Standing Working Group on Access to Medicines would provide a forum for considering public health issues and rights of people in both of these processes.

The proposed working group on access to medicines would examine a number of important issues in the implementation of the existing TRIPS Agreement, such as:

• Compulsory licensing of patents, as permitted under Article 31 of the TRIPS Agreement. The working group would work with the Council for TRIPS and other WTO bodies to review a number of issues concerning intellectual property rules, as they relate to operation.

• Allowing for exceptions to patent rights (under Article 30 of TRIPS) for production of medicines for export markets when the medicine is exported to a country with a compulsory licence. This would ensure that countries with small domestic markets can benefit from compulsory licensing.

• Allowing for exceptions to patent rights (under Article 30 of TRIPS) for medical research, so that patents are not used to stop research and hamper the introduction of generic medicines.

General Policy Issues

• 1.3 billion people in the world live on less than US$1 per day.

• 20% of the world’s population consumes 80% of the world’s resources.

• Every 3 seconds a child dies of diseases of poverty.

• 17 million deaths per year are due to infectious disease.

• Currently, 33 million people live with HIV, and 7–8 million with active tuberculosis.

• More than 90% of all death and suffering from infectious diseases occurs in the developing world.

• 20% of the world’s population uses 80% of the worldwide production of medicines.

• 0.2% of pharmaceutical research is devoted to acute respiratory infections, tuberculosis and diarrhoea, while 18% of deaths are attributable to these diseases.

* This statement was developed at the Conference on Increasing Access to Essential Drugs in a Globalized Economy: Working Towards Solutions, which was organized by Health Action International, Médecins Sans Frontières, and Consumer Project on Technology. The Conference took place in Amsterdam, the Netherlands, November 25–26, 1999.
• Avoiding overly restrictive and anti-competitive interpretations of TRIPS rules regarding protection of health registration data or other unnecessary regulatory barriers to competition.

• Avoiding restrictive interpretations of trademark rights on issues such as generic labelling and prescribing practices.

• Assessing the impact of inadequate reviews of patentability standards (novelty and usefulness) on access to medicines.

• Recommending differential rules for essential medicines, such as simplified and fast track compulsory licensing procedures.

• Examining new paradigms for intellectual property rights and health care, including “burden sharing” approaches for research and development that permit countries to consider a wider range of policy instruments to promote research and development.

• Assessing the practical burdens on poor countries of administering patent systems and resolving disputes over rights.

National governments need to develop mechanisms to ensure funding for research and development for neglected diseases

Innovative approaches to stimulating research in essential medicines need to be devised, including:

• Increased public and donor funding of health care research.

• Compulsory research obligations, such as requirements that companies reinvest a percentage of pharmaceutical sales into research and development, either directly or through public or private sector research and development programmes.

• Development of a “Neglected Disease Act” that could be used to stimulate private investment for communicable disease vaccines and medicines.
Influenza preparedness plan: antiviral drugs

It is impossible to anticipate an influenza pandemic and, should a true influenza pandemic virus again appear as in 1918 — or even epidemics such as those experienced in the United States of America in 1976 and Hong Kong in 1997, there can be a rapid build up of public fear. Such fears create major challenges for health authorities. In order to better respond to such situations, WHO has devised an Influenza Pandemic Preparedness Plan (1).

The plan outlines the separate but complementary roles of WHO and national authorities when an influenza pandemic is imminent or actually occurs. The following abbreviated extract from the plan gives information on the drugs available to deal with outbreaks and includes information on the newly marketed anti-influenza drugs. However, vaccination remains the primary method of preventing and controlling influenza, and production and use of an influenza vaccine are discussed on pages 235–237.

Policies are needed on the role of antiviral drugs in pandemic situations. As part of planning, mechanisms should be in place to import, license and distribute these drugs and to maintain a supply for critical needs, such as for health care staff and laboratory workers who may be exposed to new strains.

Generally, antiviral drugs will be more readily available since a vaccine to combat a new strain will require a minimum of 8 months to produce. However, the issues which need to be considered before providing antiviral drugs are similar to those for vaccines: identification of target groups and distribution, dosage, availability, methods of response to a sudden increase of demand, and safety.

Until now, amantadine and rimantadine have been used to treat influenza type A and have been shown to be clinically effective when taken throughout the period of exposure in a normal epidemic or outbreak situation. They also reduce the duration of illness by 1–2 days when taken early after onset. Although their effectiveness is similar, rimantadine has a better safety record. Specifically, amantadine is excreted by the kidneys and can cause significant neurological side effects, particularly in those with diminished renal function, including generally healthy elderly persons. This does not appear to be a problem associated with rimantadine.

Both drugs interfere with the replicative cycle of influenza A (but not B) viruses through blocking the function of a membrane-spanning protein synthesized in influenza-infected cells. Each has been found to be >70% effective in preventing illness caused by influenza A virus (2). WHO recommends either drug for use when a vaccine is not yet available or has only just been administered (3).

The recommended dose of amantadine for prophylaxis and treatment is:

- **Adults:** 200 mg daily
- **Children 10–15 years and adults over 65 years:** 100 mg
- **Children 1–9 years:** 2–4 mg/kg

Caution must be exercised in the event of decreased renal function. Occasional resistance to amantadine and rimantadine can develop in viruses present in persons using the drugs to treat symptoms (4) and such drug-resistant viruses may be transmitted to contacts (5).

Other anti-influenza drugs with a different mode of action to amantadine and rimantadine and active against influenza type A and B have recently become available. Oseltamivir and zanamivir have been licensed in the United States and some European countries (6). They are two closely related compounds which bind to the active site in a protein found on the surface of influenza viruses, the enzyme neuraminidase. The binding appears extremely strong and in human clinical studies both drugs interfere with viral replication to a high degree and provide protection similar to amantadine and rimantadine. However, evidence for use of these antiviral drugs to treat influenza is based principally on studies in patients with uncomplicated influenza.
There is no clear evidence to support safety and efficacy in persons with underlying respiratory or cardiac diseases, or persons with complications which can develop during an acute influenza episode, such as bacterial pneumonia (7).

Human clinical trials have not yet been undertaken in children under 12 years of age or the elderly. Important considerations therefore need to be taken and zanamivir, in particular, needs special caution in patients with underlying asthma or chronic obstructive pulmonary disease (8). The presence of primary or concomitant bacterial infections should also be considered when making treatment decisions in patients with suspected influenza.

References
7. Safe and appropriate use of influenza drugs. CDER Public Health Advisory, 12 January 2000.
8. FDA reminds prescribers of important considerations before prescribing flu drugs. FDA Talk Paper, T00-3 (2000).

**Atovaquone and proguanil hydrochloride: a new antimalarial combination**

Atovaquone/proguanil has been shown to be effective for prophylaxis of falciparum malaria and for treatment of malaria caused by any of the four species of human malaria parasites, although the data on the efficacy for *P. vivax*, *P. malariae* and *P. ovale* are limited (1). As neither component has activity against hypnozoites of *P. vivax*, treatment of vivax and ovale malaria must be followed by primaquine to prevent relapse. The role of atovaquone and proguanil in malaria endemic countries is discussed on page 229.

The cure rates with atovaquone/proguanil were significantly higher than those with mefloquine (2), amodiaquine (3), chloroquine (1, 4) or a combination of chloroquine and sulfadoxine/pyrimethamine (1, 4) in open-label clinical trials in those countries where some resistance to these drugs existed.

Published data on the use and efficacy of atovaquone/proguanil for the treatment of falciparum malaria in children (11 kg and above) is limited to open-label trials in Kenya (5) and Thailand (6) in which the cure rates were 94% and 100% respectively. Further data are currently being obtained in specific areas of Kenya and Uganda. At present there are no data for children under 11 kg.

**Dosage**

*Tablets (adult): 250 mg atovaquone and 100 mg proguanil hydrochloride (paediatric): 62.5 mg atovaquone and 25 mg proguanil hydrochloride.*

The daily dose should be taken with food or a milky drink at the same time each day. If vomiting occurs within 1 hour of dosing, a repeat dose should be taken. The manufacturer’s dosage recommendations are as follows.

**Prophylaxis**

Prophylaxis should begin 1–2 days prior to entering a malaria-endemic region and be continued during the period of residence and for 7 days after leaving.

*Adults:* One adult tablet daily.

*Children:* 11–20 kg body weight — One paediatric tablet daily.

21–30 kg body weight — Two paediatric tablets as a single dose daily.

31–40 kg body weight — Three paediatric tablets as a single dose daily.

> 40 kg body weight — One adult tablet daily.
Treatment

**Adults:** Four adult tablets (total daily dose 1 g atovaquone/400 mg proguanil hydrochloride) as a single dose for 3 consecutive days.

**Children:**
- 11–20 kg body weight. One adult tablet daily for 3 consecutive days.
- 21–30 kg body weight. Two adult tablets as a single dose for 3 consecutive days.
- 31–40 kg body weight. Three adult tablets as a single dose for 3 consecutive days.
- > 40 kg body weight. Four adult tablets as a single dose for 3 consecutive days.

**Use in pregnancy**
The safety and efficacy of atovaquone/proguanil in the treatment and chemoprophylaxis of malaria during pregnancy have not been established. Neither component is teratogenic in animals or mutagenic in standard tests (7). A clinical trial to evaluate the combination for the treatment of falciparum malaria in pregnant women is planned for early 2000.

**Adverse effects**
The nature and frequency of adverse experiences reported in controlled clinical trials for malaria prophylaxis were similar in patients treated with atovaquone and proguanil hydrochloride or with placebo. The most commonly reported adverse events during prophylaxis were headache, abdominal pain, dyspepsia, gastritis and diarrhoea. No drug-related effects on haematological parameters or clinical chemistry were observed in these studies (8).

The nature and frequency of adverse experiences reported in controlled clinical trials for malaria treatment were generally similar in patients receiving atovaquone and proguanil hydrochloride or the comparator antimalarial drug. In some studies, vomiting occurred more often in patients treated with atovaquone and proguanil hydrochloride. The most commonly reported adverse events during treatment were abdominal pain, headache, anorexia, nausea, vomiting, diarrhoea and coughing (1).

**Contraindications**
Atovaquone/proguanil is contraindicated in individuals with known hypersensitivity to atovaquone or proguanil hydrochloride or any component of the formulation.

**Drug interactions**
Concomitant treatment with tetracycline, metoclopramide and rifampicin has been associated with significant decreases in plasma concentrations of atovaquone (9).

**References**
Current Topics

Roll Back Malaria

The impact of malaria on world health is enormous: over 1 million deaths and in excess of 300 million clinical cases each year jeopardize the economic productivity and livelihood of the world’s poorest populations. Complicated malaria can result in a 25% loss of household earnings and malaria endemic countries can lose as much as 6% in gross domestic product (GDP).

The prime objective of the Global Partnership to Roll Back Malaria is to halve the burden of malaria mortality and morbidity over the next decade through interventions adapted to local needs and by reinforcement of the health sector. The founding members of Roll Back Malaria are UNICEF, UNDP, the World Bank and WHO, with WHO acting as Secretariat. Progress has been made in harnessing worldwide commitment to the partnership from governments, research institutions, the pharmaceutical industry, nongovernmental organizations and development agencies.

Such a reduction in incidence should be achievable with existing tools but a further halving over the following decade will only be possible if new antimalarial interventions are developed. The treatment of malaria is particularly problematic given increasing drug resistance and the virtual abandonment of tropical disease research by the pharmaceutical industry.

The Medicines for Malaria Venture (MMV)

MMV’s goal is to develop and manage a portfolio of drug discovery and development projects that will yield new antimalarial products. These products will be targeted for appropriate use and affordable access by disease-endemic countries. It is estimated that the venture will require US$ 30 million per year combined with donations in kind, other resources and expertise from industrial partners to succeed. Funding will be focused on a limited number of projects but at a level considered to be adequate to achieve conclusive results. The projects will be set up in such a way that partnerships will operate between pharmaceutical companies, academic groups and public sector agencies. Products generated through this collaboration will be contracted out to companies for manufacture and commercialization.

The first three discovery research projects have now been selected on a competitive basis and funding is available for work to start immediately. These will be developed through collaboration with major pharmaceutical companies — Glaxo Wellcome with a group based at the University of Bristol, SmithKline Beecham with a team from the University of California, San Francisco, and Hoffmann-La Roche with a consortium led by the University of Nebraska. The projects were selected from over 100 proposals from 27 countries. This has increased the level of pharmaceutical industry involvement in malaria research considerably. It is anticipated that with the establishment of MMV as an independent operation in its own right and the demonstrated commitment of the pharmaceutical industry to this process, further funding will become available. In this way, it is hoped that MMV will achieve its ultimate goal of registering and commercializing one new antimalarial product every five years and in assisting in the global effort to reduce the malaria disease burden.

The Japanese alliance

Within the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), an alliance has been established between WHO, the Government of Japan and 12 Japanese pharmaceutical companies for discovery

of new types of antimalarial drugs. Plans have been
developed to screen more than 12 000 different
chemical entities from the chemical libraries of the
pharmaceutical companies in collaboration with
Kitasako Institute. Some of the chemicals in the
libraries have already provided material for medi-
cines but have never been examined for antimalar-
ial activity. The Kitasako Institute plans to screen
2000 entities each year for in vitro activity against
the intra-erythrocyte stages of chloroquine-resistant
Plasmodium falciparum. Any compounds that look
promising will enter WHO’s drug development
pipeline.

Benefits from the alliance will be the increased
resources, information and knowledge towards
antimalarial research and development, intellectual
property rights and public relations. Ultimately,
however, it will be patients who will benefit the most
since any drug passing through the WHO drug
development process will need to be affordable to
those in need.

A new antimalarial
donation programme
Malarone®, a fixed-dose combination antimalarial
of atovaquone and proguanil hydrochloride, was
first registered in the United Kingdom in 1996 for
the treatment of multidrug-resistant falciparum
malaria. It has subsequently been registered for this
indication in 32 other countries worldwide, including
7 in Western Europe. It has also been registered for
prophylaxis in Denmark. Registration in the USA for
both treatment and prophylaxis of falciparum
malaria is pending. Its role in malaria control is
being determined through public/private sector
collaboration for policy and operational research in
cooperation with the Global Partnership to Roll
Back Malaria.

The role of atovaquone and proguanil
in control programmes
There has been much discussion on whether this
combination product should be introduced for
treatment in malaria-endemic countries immediately
or whether it should be held in reserve for the future
when treatment options will be limited because of
increased resistance to existing drugs. The
application of a policy to withhold an effective drug
is difficult, although there are clearly regions (such
as West Africa) where there is little resistance to
amodiaquine and sulfadoxine/pyrimethamine and
the use of atovaquone/proguanil based solely on
efficacy criteria would not be justified. However, it is
always difficult to determine the optimal role of an
antimalarial in areas of multidrug resistance. The
issue of efficacy is only one of the factors that need
to be considered when incorporating a new drug
into a national drug policy and cost/effectiveness,
sustainable delivery, access and the potential
impact of changes on treatment policy will need to
be evaluated.

To help countries consider these issues, Glaxo
Wellcome, the manufacturers of Malarone®, have
agreed not to market the product in malaria-
endemic countries immediately. Instead, in
collaboration with the Task Force for Child Survival
and Development, they are working with the
Ministries of Health in Kenya, the United Republic
of Tanzania and Uganda to determine the
usefulness of atovaquone/proguanil for patients
who fail to respond to the standard treatment at the
district hospital level. Thereafter, the product is
provided free of charge to eligible patients through
the “Malarone Donation Programme”. The donation
programme also aims to define the role of
atovaquone/proguanil in reducing severe anaemia
in children, morbidity and mortality in pregnant
women and in patients with drug-resistant disease.
Product information is set out on page 226.

The Programme is being implemented within the
context of the Global Partnership to Roll Back
Malaria and the objectives are fully supported by
WHO. Once the role of atovaquone/proguanil in
national drug policy is defined, and if anticipated
demand for the drug exceeds the quantity which
Glaxo Wellcome has offered to donate, the Global
Partnership to Roll Back Malaria will seek ways to
reduce the cost for public sector use.

Roll Back Malaria in Europe
The campaign to combat malaria launched in the
late 1950s eradicated malaria in all countries of the
WHO European Region, except for the Asian part
of Turkey and residual foci in Azerbaijan and
Tajikistan. By the 1980s, malaria was very nearly a
forgotten disease in the Region, but in recent years
it has experienced a dramatic resurgence owing to
political and economic instability, massive popula-
tion movements and the impact of large-scale
irrigation projects.

In 1993, some 30 years after the eradication of
malaria in the former Union of Soviet Socialist
Republics (USSR), some 1000 cases of malaria
were registered in the Russian Federation and in the Newly Independent States (NIS). Epidemiological surveillance revealed that the 318 cases in Belarus, Kazakhstan, the Russian Federation and Ukraine were all imported, while the 672 cases detected in Azerbaijan, Tajikistan, Turkmenistan and Uzbekistan, were indigenous.

Since 1993, the epidemiological situation relating to malaria has deteriorated considerably: currently, large-scale malaria epidemics are in progress in Azerbaijan, Tajikistan and Turkey, while Armenia is experiencing a small epidemic and an outbreak has occurred recently in Turkmenistan. The number of registered cases peaked in 1997, when 77,985 indigenous cases were officially reported in the region. These were caused almost exclusively by *Plasmodium vivax*, *P. falciparum* being restricted to a limited number of cases in Tajikistan.

The increasing number of cases of imported malaria has also raised the question of the risk of the re-introduction of malaria into some areas of Europe. Where efficient vectors exist, as in Southern Europe, the risk of reappearance of the disease is considered to be real but improbable given the efficient malaria surveillance network of public health services and early detection and treatment of malaria cases.

The WHO Antimicrobial Resistance Information Bank

Despite the enormous advances in health care made during the last half-century, infectious diseases still account for 25% of mortality worldwide and 45% in low-income countries. Anti-infective drugs are critically important in reducing the global burden of diseases such as tuberculosis, acute respiratory infections, malaria, sexually transmitted diseases or hospital-acquired infections. However, as resistant microbes develop and spread, the effectiveness of these drugs is diminished.

In order to define more clearly the magnitude of the resistance problem and the global impact on mortality, morbidity and health care costs, WHO has been requested to undertake a number of surveillance, education, policy development and implementation activities. These have now been extended to include anti-infective drug resistance surveillance and containment.

It is only by the more careful use of anti-infective drugs that emergence and spread of resistance will be contained. This will require the collaboration of groups which include prescribers, dispensers, patients, governments and industry, including the agriculture, aquaculture and horticulture industries. As part of the new activity, the Antimicrobial Resistance InfoBank (1) will gather and make accessible information on antimicrobial resistance surveillance networks and resistance data.

Other activities supporting the data bank will include strengthening national capacity to detect, monitor and respond to anti-infective drug resistance. Together with the Food and Agriculture Organization of the United Nations (FAO) and other international organizations the health implications of anti-infective drug use in food production and other industries will continue to be investigated. Briefing materials, fact sheets and articles will be provided for education and advocacy and countries will be assisted in developing national surveillance networks.

Reference

1. A-R InfoBank is available on http://www.who.int/emc/amr.html
Vaccines and biomedicines

Quality assurance and safety of biologicals

Many of the items debated at the 50th meeting of the WHO Expert Committee on Biological Standardization (ECBS) reflect the increasing complexity of biomedicines. It seems possible that within the next few years the number of new biological medicines may supersede that of new chemical entities coming onto the market. The challenge now facing manufacturers and national regulatory authorities is how to continue to assure the quality and safety of new and existing biologicals. Biological standardization is set to play a key role in this respect.

Recommendations for oral poliovirus vaccine

Revised recommendations (formerly requirements) for production and control of oral poliovirus vaccine (OPV) were agreed by the ECBS. New quality control procedures have now been introduced with the potential to increase the stringency of control. This is an important consideration given the considerable success of the polio eradication initiative and enhanced risk/benefit considerations of OPV use. The new quality control procedures will also decrease vaccine testing time. This will speed up OPV availability and respond to increased demands for supplies of vaccine to complete the eradication programme.

For the first time, a test for molecular consistency of production for a live virus vaccine is now available. Mutant analysis by polymerase chain reaction (PCR) and restriction enzyme cleavage — MAPREC — quantifies reversion of a key base, 472C, that correlates in type 3 poliovirus vaccine with results of the WHO neurovirulence test (1). WHO-supported studies of the method have shown it to be a robust and reliable procedure. Results showed that MAPREC provided a very valuable additional test for consistency of production and the method was endorsed as the in vitro test of preference for control of poliovirus type 3. Excellent progress with MAPREC assays for poliovirus types 1 and 2 was also reported and the possibility of introducing MAPREC for these serotypes will be considered as soon as possible.

The discovery of the gene for the cellular receptor for poliovirus led to development of the TgPVR21 transgenic mouse susceptible to poliovirus infection (2, 3). A neurovirulence test for poliovirus vaccine has now been developed in the TgPVR21 transgenic mouse line and was shown in WHO-sponsored studies to be a suitable alternative to the test in monkeys for poliovirus type 3. It was therefore introduced in the new recommendations. Excellent progress with TgPVR21 neurovirulence tests for poliovirus types 1 and 2 was reported and the possibility of introducing a neurovirulence test in TgPVR21 mice for these serotypes will be considered as soon as possible.

The entire cycle from basic scientific research, through method development to standardization and application as control tests of MAPREC and the transgenic mouse model were all paradigms for regulatory research. This work clearly illustrated the need for long-term commitment of resources if significant advances in control and standardization of biologicals are to be made.

Reference reagents and panels for diagnostic procedures for TSEs

A WHO Consultation on International Reference Materials for Diagnosis and Study of Transmissible Spongiform Encephalopathies (TSEs) held in May 1999 identified the need for international harmonization and the establishment of reference reagents and panels to compare diagnostic procedures.
Reference brain-derived materials and human and animal lymphoid tissue were considered necessary to compare assay systems. A working group established by WHO to develop appropriate standards was taking steps to obtain these materials. However, preparation of these reference materials will require dedicated facilities to comply with strict levels of laboratory containment. Candidate reference materials will be characterized in bioassays and immunoassays.

**International standards**

The ECBS established 28 new or replacement International Standards and Reference Reagents covering a wide range of products (Table 1, page 234). Additionally, several International Standards, Reference Materials and Requirements that are no longer needed were discontinued following a public consultative process (Table 2, page 235) (5). The Committee also proposed to discontinue the first International Reference Preparation for protamine (salmon) at its next meeting, subject to public comment to this notice (Table 3, page 235).

**Discontinuation of requirements**

As recommended by the 49th meeting of the ECBS, the intention to discontinue the WHO Requirements for Cholera Vaccine and Smallpox Vaccine was circulated for public comment. As a consequence, it was decided that the WHO Requirements for Cholera Vaccine should be discontinued in order to ensure correct testing of the new oral inactivated vaccines. However, in the case of smallpox virus, laboratory stocks had not been destroyed as expected and the Requirements for Smallpox Vaccine were retained.

**Database and electronic publication**

Following a recommendation of the ECBS, the catalogue of WHO International Biological Standards and Reference Materials has been fully updated and made available on the Internet. The entire list of WHO biological standards and reference reagents is now available on the WHO home page at the following address:

http://www.who.int/technology/biological.html

A number of future developments concerning the new database include proposed linkages to the custodian laboratory holding the standards and to the corresponding WHO documents and publications and reports in the scientific literature.

**Other activities**

The ECBS endorsed several other new projects including new or replacement reference materials for pertussis toxin and quality control of nucleic acid amplification tests (parvovirus B19 DNA, hepatitis A RNA, HTLV-1 RNA and HTLV-2 RNA). The Committee was also updated on many projects that are in progress. These included evaluation of mouse protection models for acellular pertussis vaccines; harmonization of antigen content and potency measurement of diphtheria and tetanus vaccines; standardization and control of oral cholera vaccines; standardization of antibody measurement; development of guidelines on preclinical and clinical testing of vaccines; abnormal toxicity test; consideration of the use of thiomersal as a preservative in vaccines, and evaluation of safety issues associated with the use of cell substrates for vaccine production.

Ongoing activities for blood and plasma derived products include a project on quality assurance of plasma-derived medicinal products and plasma fractionation activities; quality control of virus markers (HBsAg, anti-HCV and anti-HIV) in blood screening; standardization of unfractionated heparin and development of new international reference materials for blood grouping reagents.

Progress in standardization of biological therapeutics was also reported and the Committee endorsed proposals to establish new reference materials for vascular endothelial growth factor, ciliary neurotrophic factor, keratinocyte growth factor, neurotrophin-3 and relaxin. Given the rapidly expanding cytokines sector and limited resources available to carry out these activities, the Committee considered a policy to prioritize work in this area. A decision tree, developed during a WHO Consultation on Cytokine Standards, was modified for use in prioritizing work for all categories of biologicals.

**References**


### Table 1. International biological standards and reference reagents established by the 50th WHO Expert Committee on Biological Standardization

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Activity</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibodies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Islet cell antibodies</td>
<td>20 units/ampoule</td>
<td>First Reference Reagent 1999</td>
</tr>
<tr>
<td></td>
<td>100 units/ampoule of anti-GAD65</td>
<td>First Reference Reagent 1999</td>
</tr>
<tr>
<td></td>
<td>100 units/ampoule of anti-IA-2</td>
<td>First Reference Reagent 1999</td>
</tr>
<tr>
<td>Anti-pertussis serum, mouse</td>
<td>17 units per vial of anti-pertussis toxin</td>
<td>First Reference Reagent 1999</td>
</tr>
<tr>
<td></td>
<td>143 units per vial of anti-filamentous</td>
<td>First Reference Reagent 1999</td>
</tr>
<tr>
<td></td>
<td>haemagglutinin</td>
<td>First Reference Reagent 1999</td>
</tr>
<tr>
<td></td>
<td>30 units per vial of anti-pertactin</td>
<td>First Reference Reagent 1999</td>
</tr>
<tr>
<td></td>
<td>32 units per vial of anti-fimbriae types 2/3</td>
<td>First Reference Reagent 1999</td>
</tr>
<tr>
<td><strong>Antigens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate specific antigen (PSA)</td>
<td>1 µg total PSA per vial</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td>Prostate specific antigen (90:10)</td>
<td>1 µg total PSA per vial</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td>Diphtheria toxoid, adsorbed</td>
<td>160 IU/ampoule</td>
<td>Third International Standard 1999</td>
</tr>
<tr>
<td>Hepatitis A vaccine, inactivated</td>
<td>100 IU/ml of immunogenic activity;</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td></td>
<td>100 IU/ml of antigen content</td>
<td></td>
</tr>
<tr>
<td><strong>Blood products and related substances</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood coagulation factors II and X</td>
<td>11.2 IU/ampoule of factor II</td>
<td>Third International Standard 1999</td>
</tr>
<tr>
<td></td>
<td>10.2 IU/ampoule of factor X</td>
<td>Third International Standard 1999</td>
</tr>
<tr>
<td>Blood coagulation factor IXa,</td>
<td>11.0 IU/ampoule</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td></td>
<td>concentrate, human</td>
<td></td>
</tr>
<tr>
<td></td>
<td>concentrate, human, recombinant</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen, plasma, human</td>
<td>2.2 mg/ml</td>
<td>Second International Standard 1999</td>
</tr>
<tr>
<td>Tissue plasminogen activator,</td>
<td>10 000 IU/ampoule</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td></td>
<td>recombinant (alteplase)</td>
<td></td>
</tr>
<tr>
<td>Human immunodeficiency virus type-1 RNA</td>
<td>100 000 IU/vial</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td>Hepatitis B virus DNA</td>
<td>500 000 IU/vial</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td><strong>Cytokines, growth factors and endocrinological substances</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin-like growth factor-II,</td>
<td>5000 units per ampoule</td>
<td>First Reference Reagent 1999</td>
</tr>
<tr>
<td>human, recombinant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocyte growth factor/</td>
<td>4000 IU/ampoule</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td>scatter factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocyte growth factor/</td>
<td>2000 IU/ampoule</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td>scatter factor (precursor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptin, human</td>
<td>4000 IU/ampoule</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td>Leptin, mouse</td>
<td>4000 IU/ampoule</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td>Calcitonin, salmon</td>
<td>138 IU/ampoule</td>
<td>Third International Standard 1999</td>
</tr>
<tr>
<td>Interferon alpha, human leukocyte</td>
<td>11 000 IU/ampoule</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td>Interferon omega, human</td>
<td>20 000 IU/ampoule</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td>Interferon alpha 2c, human</td>
<td>40 000 IU/ampoule</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td>Interferon alpha 2b, human</td>
<td>70 000 IU/ampoule</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td>Interferon alpha concensus, human</td>
<td>100 000 IU/ampoule</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>38 000 IU/ampoule</td>
<td>First International Standard 1999</td>
</tr>
<tr>
<td>lymphoblastoid N1, human</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon alpha 2a, human</td>
<td>63 000 IU/ampoule</td>
<td>Second International Standard, 1999</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>60 000 IU/ampoule</td>
<td>First International Standard, 1999</td>
</tr>
<tr>
<td>(leukocyte N3), human</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon alpha-1/8, human</td>
<td>27 000 IU/ampoule</td>
<td>First International Standard, 1999</td>
</tr>
<tr>
<td>Chorionic gonadotrophin</td>
<td>650 IU/ampoule</td>
<td>Fourth International Standard, 1999</td>
</tr>
</tbody>
</table>
### Table 2. Reference materials discontinued by the 50th WHO Expert Committee on Biological Standardization

<table>
<thead>
<tr>
<th>Reference Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The First International Reference Reagent for adenovirus antisera, equine types 1, 2, 3, 5, 6, 7a, 8, 9, 10, 11, 13, 15, 17.</td>
</tr>
<tr>
<td>The First International Reference Reagent for adenovirus antisera, equine types 4, 19, 20, 22, 23, 24.</td>
</tr>
<tr>
<td>The First International Reference Reagent for adenovirus antisera, equine types 12, 18.</td>
</tr>
<tr>
<td>The First International Reference Reagent for adenovirus antisera, equine types 25, 26, 27, 28, 29, 30, 31, 32 and 33.</td>
</tr>
<tr>
<td>The First International Reference Reagent for adenovirus antisera, equine types 34, 35, 36.</td>
</tr>
<tr>
<td>The First International Standard anti-A,B blood typing serum, human.</td>
</tr>
<tr>
<td>The First International Reference Reagent for anti-HBs/ad serum, goat.</td>
</tr>
<tr>
<td>The First International Reference Reagent for anti-HBs/ad serum, guinea-pig.</td>
</tr>
<tr>
<td>The First International Reference Reagent for anti-HBs/ar serum, rabbit.</td>
</tr>
<tr>
<td>The First International Reference Reagent for anti-HBs/ay serum, goat.</td>
</tr>
<tr>
<td>The First International Reference Reagent for anti-HBs/ay serum, guinea-pig.</td>
</tr>
<tr>
<td>The First International Standard FITC-conjugated sheep anti-human immunoglobulins.</td>
</tr>
<tr>
<td>The First International Standard FITC-conjugated sheep anti-human IgG (anti-gamma chain).</td>
</tr>
<tr>
<td>The First International Standard FITC-conjugated sheep anti-human IgM (anti-mu chain).</td>
</tr>
<tr>
<td>The First International Standard for Thrombin, human.</td>
</tr>
<tr>
<td>The First International Reference Preparation for interferon, human, leukocyte (HuIFN-a (Le)).</td>
</tr>
<tr>
<td>The First International Reference Reagent for interferon, human, recombinant (rHuIFN-alpha2(alpha2b)).</td>
</tr>
<tr>
<td>The First International Standard for interferon, human, lymphoblastoid (Namalwa) (HuIFN-alpha (Ly)).</td>
</tr>
<tr>
<td>The First International Reference Standard for interferon, human, rDNA (rHuIFN-alpha2 (alpha-A)).</td>
</tr>
<tr>
<td>The First International Working Standard for interferon, human, leukocyte (HuIFN-alpha (Le)).</td>
</tr>
<tr>
<td>The First International Standard for candicidin.</td>
</tr>
<tr>
<td>The First International Standard for rolitetracycline.</td>
</tr>
<tr>
<td>The First International Standard for desmopressin.</td>
</tr>
<tr>
<td>The First International Reference Preparation for gonadorelin.</td>
</tr>
<tr>
<td>The First International Reference Preparation for nisin.</td>
</tr>
<tr>
<td>The First International Reference Preparation for parathyroid hormone, bovine, for bioassay.</td>
</tr>
</tbody>
</table>

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

**Blood products**

<table>
<thead>
<tr>
<th>Reference Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The First International Reference Preparation for protamine (salmon) (1954)</td>
</tr>
</tbody>
</table>

Comments on this proposal should be forwarded by 30 September 2000 to:
Dr E Griffiths, Quality Assurance and Safety of Biologicals, World Health Organization,
1211 Geneva 27, Switzerland, Fax +41 22 791 4210
Influenza preparedness plan: vaccine production and availability

Influenza virus vaccines can take a minimum of 8 months to produce from the moment that a pandemic is identified to availability of a new vaccine. For this reason, WHO has devised an Influenza Pandemic Preparedness Plan (1) which outlines the separate but complementary roles of WHO and national authorities when an epidemic or pandemic is imminent or actually occurs. The following extract from the plan gives information on how any delay in influenza vaccine production can be minimized and also advises on how vaccine can be prepared for the following season.

Influenza virus vaccines are normally made by growing approved seed viruses in embryonated chicken eggs, purifying and chemically treating the harvest, including inactivating infectivity, and then adjusting the concentration against reference biological standards. In the case of a pandemic virus, however, special issues arise concerning vaccine composition that must be addressed before vaccine production can be completed. The lead-time from identifying a new strain to beginning vaccine production is usually 2–3 months, and vaccine lots first become available within about 4–5 months of inoculation of eggs.

Influenza epidemics usually peak between December and March in the northern hemisphere, and June and September in the southern hemisphere. To allow for the production of vaccines to be used before the winter season, a WHO meeting to select strains for vaccines takes place in February each year for the northern hemisphere, and in September for the southern hemisphere.

In some cases, newly recommended strains do not grow well in the embryonated chicken eggs used for vaccine production, so “high growth reassortant viruses” (hgr viruses) must be made. Once the WHO recommendation is known, vaccine production processes can begin immediately if the vaccine is multivalent and contains at least one previously used strain. Development of seeds suitable for production of new strains can be completed during this same time period. However, in a pandemic situation it is likely that monovalent vaccine would be made. In this case, efforts to reduce time for development of seed viruses should be actively pursued since all other activities are dependent on this phase.

Reducing vaccine production time

Early preparation of vaccine production seeds:
If possible, production seeds (“reassortants”) should be developed for killed and live attenuated vaccines (where licensed) as soon as pandemic viruses are detected and in advance of deciding whether they are needed. Under optimal circumstances this might be done in as little as 3–4 weeks. However, the H5N1 virus isolated from cases in Hong Kong in 1997 created several unanticipated difficulties because of its pathogenicity for chickens and embryonated chicken eggs, as well as the high case-fatality rate among infected people in Hong Kong. There was therefore a need for laboratories receiving the original isolates to have approved biological containment facilities and procedures which would protect laboratory workers and prevent any possible release of the virus into the environment. Contingency planning for future pandemic threats should include measures to ensure that the necessary laboratory facilities and procedures exist in numerous sites, including those involved in developing vaccine seeds or manufacturing processes.

Time-saving approaches
Normally, 4–8 weeks are needed to produce SRD reagents for standardizing killed influenza virus
vaccines. It may be possible to reduce this time to one week if SRD reagents to potential pandemic strains are stockpiled, for example, reference strains for all haemagglutinin sub-types. An alternative would be to attain consensus that would allow different potency tests to be used. One possibility, in this regard, might be the determination of the amount of viral haemagglutinin by procedures, that do not use subtype-specific immunological reagents.

**Reduce delays in licensing of vaccines**

More than one national control authority may be involved in approving the release of vaccine, since vaccines are used in many countries. Agreements on central licensing of vaccines for distribution in multiple countries could overcome this problem.

**Develop alternative production procedures**

Orders for eggs to produce vaccines by current technology must be made at least 6 months in advance of production beginning. This may cause difficulties if a pandemic virus emerges outside the normal time when vaccine production is planned. Alternative methods of production based on fermentation technology, such as virus growth in tissue culture or antigen production by recombinant DNA technology, should be pursued.

**Establish a research agenda**

It is possible that other approaches to vaccination may improve effectiveness. Live attenuated vaccines already offer the potential to immunize with a single dose those who have never experienced the antigens contained in the vaccine. This would appear to be a potentially important advantage in a pandemic, but needs further consideration and research, including addressing any special concerns arising from the introduction of a new haemagglutinin subtype in an infectious influenza vaccine during a pre-pandemic period. Mixing traditional vaccines with adjuvants may improve immunogenicity, and again could eliminate the need for two doses in unprimed populations, possibly also reducing the amount of antigen needed for each dose.

DNA vaccines represent another possibility of providing large numbers of doses in a short time. Since it is not known when the next pandemic will take place, intensive research could considerably improve the approaches available.

**Vaccine valency**

*Standardize pandemic virus vaccine to be monovalent*

Since 1977, WHO has recommended that influenza vaccines be trivalent, containing one type A(H3N2) virus, one type A(H1N1) virus and one type B virus. When responding to a pandemic threat, decisions must be taken whether the pandemic virus vaccine will be used alone or in combination with one or more other viruses. This will depend on surveillance results and best judgement at the time. If it is felt necessary for WHO or individual countries to recommend multivalent vaccines due to uncertainty about the disappearance of former strains, this could reduce the total supply of vaccines against the pandemic virus and complicate the international sharing of vaccines.

**Purchasing and distribution**

*Plan for emergencies when negotiating vaccine procurement contracts*

Many national governments and major pharmaceutical distributors have yearly contracts with manufacturers for influenza vaccines. In the event of a pandemic, those vaccines may prove unneeded, even though manufacturers may have begun or completed their production. Each vaccine manufacturer should discuss with the country(ies) where the influenza vaccine is usually produced or distributed how such contingencies can be addressed and in an emergency the expected rate of production. Production targets may depend on the type of packaging, single-dose or multidose vials, whether split vaccines or whole virus vaccines will be produced, and the potency of the vaccine. In preparing for a pandemic, it may be desirable to build flexibility into procurement procedures to allow for different vaccination strategies. Thus, a decision might be made in advance to have contracts permitting the emergency production of multidose vials of vaccine containing 7 µg per dose instead of the usual 15 µg to allow for stretching supplies or for a schedule of two 7 µg doses instead of one dose of 15 µg in order to maximize immune response in populations lacking prior exposure to an antigen related to that of the pandemic strain.

*Explore possibilities for a “clearing house” to balance purchases and deliveries versus supply*

Each government and vaccine supplier will need to consider how much vaccine they will guarantee to purchase or sell in an emergency situation. The cost per dose may be different if vaccine is being
purchased by governments and made available to recipients without cost, or if vaccine is to be purchased at the user's expense. Without a clearing house to balance demand and supply, cost considerations rather than public health may drive vaccine distribution needs. The needs of non-industrialized countries without any resources to purchase vaccines may be completely overlooked. A mechanism such as a central clearing house operated and funded by a group of countries might allow for vaccine purchases to be pooled and distributed more equitably than otherwise. Such a system could also ensure that a portion of vaccines is purchased as a humanitarian donation for use by designated population sectors in non-industrialized countries, such as health care workers, pregnant women or others with high risk of exposure or severe disease who play essential roles in society.

**Design approaches to vaccine distribution that will be appropriate for an emergency situation**

Different countries have different systems of administration. These procedures may need modification in a pandemic situation. Plans will be needed on whether vaccine distribution will proceed only from facilities under direct government jurisdiction or through private distribution channels. Potential problems in ensuring vaccine security and accountability need to be considered. Timely and up-to-date statistics on vaccination supplies and use will be needed to guide the provision of a product expected to be in high demand and short supply. Control of stolen and counterfeit vaccines is likely to be a new problem.

**Establish international cooperation for assessing safety of influenza vaccines**

Considerable problems can develop if inappropriate reports are made of vaccine-related adverse reactions or failure to detect risks from a new vaccine that is to be widely used over a short period of time. As information travels rapidly, international cooperation is highly desirable to ensure immediate reporting of events.

**Thiomersal: theoretical risk leads to phasing out**

Thiomersal, or mercurothiolate, has been used since the 1930s to prevent bacteria and other organisms from contaminating vaccines, especially in opened multidose vials. With the possible exception of minor skin sensitivity reactions, no adverse effect following immunization has been attributed to thiomersal in all this time and its use over the years has made a valuable contribution to vaccine safety. Now, public opinion has turned firmly against the use of mercury of any sort, and there is a need to minimize exposure to this chemical from all sources.

WHO supports a statement made on 7 July 1999 by the American Academy of Pediatrics and the United States Public Health Service regarding the prospective phasing out of thiomersal. However, because there are currently no tested, efficacious and safe alternatives, WHO will continue recommending procurement of vaccines that contain the preservative. This approach has been endorsed by the WHO Expert Committee on Biological Standardization (see page 232). Although, thiomersal poses a theoretical risk of neurodevelopmental toxicity in infants, the known risk of morbidity and mortality from vaccine-preventable diseases and of contaminated multidose vaccine vials far outweighs any potential risk posed by thiomersal.

WHO and other agencies have begun the process of reducing and removing thiomersal from vaccines and within the next three years modifications to existing strategies will result in a reduction in exposure to thiomersal. Beyond three years, efforts will be focused on new vaccine-delivery technologies, alternative preservatives and combination vaccines. This will further reduce and possibly eliminate thiomersal from vaccines.

**Reference:** *Weekly Epidemiological Record, 75*:12–16 (2000).
Regulatory and Safety Matters

Leflunomide: pancytopenia and skin reactions

European Union — Leflunomide (Arava® Hoechst Marion Roussel) was granted marketing approval by the European Commission on 2 September 1999 and has been marketed in the United States since 1998. It is indicated for the treatment of active rheumatoid arthritis in adults as a disease-modifying antirheumatic drug (DMARD). An estimated 76 000 patients have been treated worldwide. To date, reports have been received of 16 cases of pancytopenia and 9 cases of serious skin reactions.

The haematological reactions may be caused by direct toxicity of the slowly eliminated active metabolite of leflunomide. Early symptoms include paleness, tiredness, increased proneness to infections and bruising. Most of the haematological reactions occurred when leflunomide was administered concomitantly or following treatment with another DMARD such as methotrexate.

Occurrence of skin reactions may be the consequence of a hypersensitivity reaction to the compound. Skin rash may include mucous membrane lesions (e.g. in the mouth) and could progress into severe, sometimes life-threatening bullous reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme.

As an urgent measure, the prescribing and patient information have been modified to include appropriate warnings and instructions.


Didanosine and pancreatitis

The manufacturer of Videx® (didanosine), a nucleoside analogue reverse transcriptase inhibitor indicated for the treatment of HIV-1 infection has reinforced the labelling to include a revised warning of fatal and non-fatal pancreatitis.

The following warning is now included in the approved product labelling. "Fatal and non-fatal pancreatitis has occurred during therapy with Videx® used alone or in combination regimens in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression. Videx® should be suspended in patients with suspected pancreatitis and discontinued in patients with confirmed pancreatitis."

"Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including didanosine and other antiretrovirals."

Reference: Communication to WHO from Food and Drug Administration, USA, 22 November 1999.

Sertraline for post-traumatic stress disorder

United States of America — The Food and Drug Administration has approved sertraline as the first drug treatment for post-traumatic stress disorder, long recognized as an important clinical problem.

The effectiveness of sertraline for treating symptoms of this disorder is based on two trials in adults diagnosed with post-traumatic stress disorder. However, the overall positive outcome appeared to have little effect in male subgroups. The importance of this apparent gender difference is unknown.


Pemoline withdrawal following liver complications

Canada — Health Canada is advising patients taking pemoline to contact their physicians as soon as possible to discuss changing to alternative treatments. The manufacturer has recalled this product which has now been withdrawn from pharmacies.

Pemoline is used to treat Attention Deficit Hyperactivity Disorder (ADHD) in children and adults together with other therapies to manage behav-
journal symptoms. To date, 16 cases of severe liver complications have been reported worldwide which may possibly be associated with this product.

Although alternative drugs exist which are safe and effective, the product will continue to be available through the special access programme, with instructions on liver function monitoring. Health Canada will evaluate new safety data as they become available.


Levetiracetam: new drug for epilepsy

United States of America — The Food and Drug Administration has approved levetiracetam for partial onset seizures in adults for use with other epilepsy medications. Unlike most epilepsy drugs, levetiracetam (as well as gabapentin) is not metabolized through the liver and is unlikely to cause interactions with other epilepsy drugs or commonly used drugs such as oral contraceptives. No serious blood or liver-related toxicities have been reported in clinical trials so far.

Patients should be advised that levetiracetam may cause dizziness and somnolence.


Methotrexate: monitoring essential

United States of America — The manufacturers of Rheumatrex® (methotrexate sodium) have advised of new information concerning product labelling.

Rare reports have been received of bone and soft tissue necrosis following radiation therapy in patients receiving methotrexate. Actual risk has not been established. There have also been rare reports of painful plaque erosion in patients treated for psoriasis. Hepatotoxicity is a known potential adverse reaction associated with methotrexate therapy and concomitant use with other hepatotoxic agents may increase risk.

Most adverse reactions are reversible if detected early. When such reactions do occur the drug should be reduced or discontinued and appropriate corrective measures taken as set out in the new labelling.

Reference: Communication to WHO from US Food and Drug Administration, 1 December 1999.

Methotrexate: care in prescribing

Australia — The Australian Adverse Reactions Advisory Committee has called attention to the risk of serious illness and death through medication errors involving methotrexate. Currently, different strengths of tablets ranging from 2.5 mg to 10 mg are available and patients may be supplied with two strengths to make up a particular dose. Medication errors have been reported in both dispensing and in patient administration of the wrong strength.

Dose frequency can create a separate source of risk. In the treatment of some diseases such as rheumatoid arthritis and psoriasis, the patient is often told to take a dose once a week. It is suggested that in this case a specific day should be identified and noted on the label at dispensing.


Grepafloxacin withdrawal: severe cardiovascular events

Glaxo Wellcome has announced that it is voluntarily withdrawing the oral fluoroquinolone antibiotic, grepafloxacin, with immediate effect. Since marketing in 1997, a small number of severe cardiovascular events have been reported. While this incidence is infrequent, the company no longer feels that the benefits of grepafloxacin outweigh the potential risk in view of the current availability of alternative antibiotics.

Grepafloxacin was indicated for the treatment of a variety of infections, including pneumonia, bronchitis and sexually transmitted bacterial infection. It has been marketed in 30 countries worldwide under the tradename Raxar® or Vaxar®.


Reteplase incompatible with heparin

European Union — Reteplase (Rapilysin®) has been marketed in 15 European Union countries since 1996 for thrombolytic therapy of acute myocardial infarction for use within 12 hours of onset of symptoms. The European Medicines Evaluation Agency (EMEA) has received 4 reports concerning a precipitation of reteplase suspected to be due to an incompatibility with heparin when combined in intravenous solution.
As a similar risk for other incompatibilities may also exist, no other medication should be added to the reteplase injection solution. As an urgent measure, the prescribing and patient information has been modified accordingly.


Postmarketing system to be revised

Japan — The Ministry of Health and Welfare has announced a complete revision of the postmarketing surveillance system in early 2000. The rule that clinical experience investigations should cover a minimum of 3000 cases will be abolished. Instead, pharmaceutical companies will be required to provide their product to a limited number of medical institutions for three months following launch of a product and conduct focused postmarketing surveillance. After inspection of the results of this surveillance, companies will be allowed to expand the number of medical institutions using the product. Requiring companies to limit sales to a small number of medical institutions and collecting information in this way will make it easier to respond to adverse drug reactions of newly approved products.

As a component of the revision, information will also be collected on medication errors such as those caused by easily confused drug names, labelling or appearance of drugs.


Abacavir: hypersensitivity reactions

European Union — Abacavir was approved for sale within the European Union in July 1999 as an antiretroviral combination therapy for the treatment of HIV-infected adults. The European Medicines Evaluation Agency (EMEA) has now carried out a review of safety information received to date and wishes to draw attention to the following:

- Prescribers must ensure that patients are fully informed of the possibility of hypersensitivity reactions which may present as flu-like illness or respiratory disease.
- Abacavir must never be restarted in patients who have shown, or who it is thought may develop, hypersensitivity reactions.

Hypersensitivity reactions are major points of concern and serious reactions are characterized by the appearance of symptoms indicative of multi-organ system involvement. Reactions usually occur within 6 weeks of initiation of treatment.

Reference: EMEA Public Statement on Abacivir (Ziagen®) — important safety information on hypersensitivity reactions and respiratory symptoms. 24 January 2000.

Initiative to curb illegal sale of drugs over the Internet

United States of America — A new initiative to protect consumers from the illegal sale of pharmaceuticals over the Internet has been proposed by the President of the USA. The initiative will include new Federal requirements for all Internet pharmacies to ensure that they comply with state and federal laws. It strengthens the current penalty structure for illegal pharmaceutical sales over the Internet by proposing a new civil penalty of US$500 000 for each violation of the sale of a prescription drug to an individual without a valid prescription. Two other major components strengthen the investigative processes and administrative subpoena authority of the Food and Drug Administration.

A new public education campaign on the potential dangers of buying prescription drugs on-line will be launched. In the opinion of the initiative, fly-by-night pharmacies put on-line consumers at increased risk for adverse reactions, dangerous drug interactions or contaminated drugs. The proposal will enable consumers to identify legitimate Internet pharmacy sites. In turn, sites will have to demonstrate their compliance with Federal and State law before they receive approval from the Food and Drug Administration to operate.

Reference: The White House, Office of the Press Secretary, 28 December 1999.

Unapproved HIV test kits available on the Internet

United States of America — The Federal Trade Commission and the Food and Drug Administration (FDA) have taken law enforcement action against the illegal promotion and sale of unapproved HIV test kits on the Internet. The tests have been pro-
moted as “rapid tests” providing home results in 15 minutes or less. However, the FDA has tested these kits and found them unreliable in detecting the presence of HIV.

Currently, only one HIV home collection test system has been approved by the FDA which allows consumers to collect a blood sample for testing which is then sent with a personal identification number to a laboratory for analysis.


V-King®: unapproved use of sildenafil

Canada — Health Canada is warning consumers not to use V-King (Extra)® capsules. Promoted as natural health products, they may contain sildenafil citrate, a prescription-only drug approved for male erectile dysfunction. Inappropriate use of sildenafil can cause severe adverse reactions and the drug should not be used by persons taking nitrate-containing products concurrently since this could result in the development of potentially life-threatening low blood pressure.

The labelling indicates the ingredients as Harp seal reproductive organ extracts, traditional Chinese herbs, and supplements. V-King® has not been assessed by Health Canada, which attributes an eight-digit drug identification number on licensing.


Miralex®: undeclared corticosteroid

Canada — Health Canada is warning users of Miralex® cream to contact a health care provider as soon as possible. Promoted on the Internet as a naturally derived product, Miralex® has been found to contain clobetasol, a prescription-only corticosteroid. The company has agreed voluntarily to stop sale of the product.

Miralex® cream may have been used for psoriasis, which should be treated under the supervision of a health care practitioner. However, suddenly stopping use of steroid-containing products may cause the more common form of plaque psoriasis to convert to pustular psoriasis.

For other skin indications, steroid-containing products can cause thinning of the skin and dilatation of blood vessels.

Health Canada has also issued a nationwide import alert for detention of Miralex® cream at all border entry points.


Rules for dietary supplements finalized

United States of America — The Food and Drug Administration has published its final rule defining the types of statements that can be made concerning the effect of a dietary supplement on the structure or function of the body. This rule describes how disease claims can be distinguished from structure/function claims. Although this rule will not affect the availability of dietary supplements, it may affect whether certain claims can be made and will result in some labelling changes.

As an example, the rule precludes express and implied disease claims, but permits claims that do not relate to disease. Serious conditions such as ageing, pregnancy, and menopause will continue to be treated as diseases.

Publication of the rule is an important part of the FDA’s overall dietary supplement strategy aimed at providing consumers with a high level of confidence in the safety, composition and labelling of dietary supplements.

The following temporary classifications were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 27 and 28 October 1999. Comments on or objections to the classification should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, P.O. Box 100, Veivet, 0518 Oslo, Norway (telephone: 0047 22 16 96 11, fax: 00 47 22 16 98 18, e-mail: whocc@nmd.no). The new ATC codes and DDDs will be included in the January 2001 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

### New ATC level codes (other than 5th level):
- Artemisinin and derivatives
- Nitrofuran derivatives

### Change of level name:
**Previous:**
Quinine alcaloids

**New:**
Methanolquinolines

### New ATC 5th level codes:
- ancrad: B01AD09
- arteether: P01BE04
- artemether: P01BE02
- artemether, combinations: P01BE52
- artemisinin: P01BE01
- artesunate: P01BE03
- atosiban: G02CX01
- bexarotene: L01XX25
- codeine, combinations with psycholeptics: N02AA79
- collagenase: D03BA03
- dermatan sulfate: B01AX04
- desloratadine: R06AX27
- dihydroartemisinin: P01BE05
- dronabinol: A04AD10
- gentamicin: S02AA14
- *Haemophilus influenzae* B and hepatitis B: J07CA08
- imidapril: C09AA16
- insulin aspart: A10AB05
- interferon alfacon-1: L03AB09
- levosimendan: C01CX08
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**ATC code changes:**

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<td>G04AB05 J01MB06</td>
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<td>methenamine</td>
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<td>G04AH01 J01RA02</td>
<td>methenamine and sulfonamides</td>
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* the products should be classified according to the J group on general anti-infectives for systemic use.

**ATC codes under revision:**

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<td>J01GB01</td>
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**New DDDs:**

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* Temporary ATC codes
** previously chlorpheniramine.

**Change of DDDs:**

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<td>sumatriptan</td>
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<td>mg</td>
<td>O</td>
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</table>
ATC/DDD Classification (final)

The following temporary classifications were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 27 and 28 October 1999. Comments on or objections to the classification should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, P.O. Box 100, Veivet, 0518 Oslo, Norway (telephone: 00 47 22 16 96 11, fax: 00 47 22 16 98 18, e-mail: whocc@nmd.no) before 1 February 2000. If no objections are received before this date, the new ATC codes and DDDs will be considered final and be included in the January 2001 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

New ATC level codes (other than 5th levels):
- Cholinesterase inhibitors: N06DA
- Anti-dementia drugs: N06D
- Antigonadotropin-releasing hormones: H01CC
- Monoclonal antibodies: L01XC
- Neuraminidase inhibitors: J05AH
- Other anti-dementia drugs: N06DX
- Other specific antirheumatic agents: M01CX

New ATC 5th level codes:
- alitretinoin: L01XX22
- amprenavir: J05AE05
- androstanolone: G03BB02
- betamethasone and antiinfectives: S03CA06
- brinzolamide: S01EC04
- bufexamac: M01AB17
- cetrimonium bromide: R02AA17
- cetrorelix: H01CC02
- chloramphenicol: S03AA08
- cinnarizine, combinations: N07CA52
- ciprofloxacin: S03AA07
- diphtheria, hepatitis B, tetanus: J07CA07
- etanercept: L04AA11
- flutrimazole: D01AC16
- framycetin: R01AX08
- gadobenic acid: V08CA07
- galantamine: N06DA04
- ganciclovir: S01AD09
- ganirelix: H01CC01
- glyceryl trinitrate: D03AX07
- hexamidine: R02AA18
- infliximab: L04AA12
- irbesarten and diuretics: C09DA04
- isosorbide dinitrate: D03AX08
New ATC 5th level codes (continued)

ketotifen S01GX08
levodropropizine R05DB27
memantine N06DX01
miconazole, combinations D01AC52
moxifloxacin J01MA14
moexipril and diuretics C09BA13
norgestimate and estrogen G03FA13
olopatadine S01GX09
oseltamivir J05AH02
oxaceprol M01AX24
pantoprazole, amoxicillin and clarithromycin A02BD04
permethrin, combinations P03AC54
pioglitazone A10BG03
policosanol C10AX08
prednisolone, combinations R01AD52
propentofylline N06BC02
rabeprazole A02BC04
repaglinide A10BX02
rosiglitazone A10BG02
sirolimus L04AA10
sodium folinate V03AF06
sodium phosphate A06AD17
technetium (99mTc) arcitumomab V09IA06
tiemonium iodide and analgesics A03DA07
trastuzumab L01XC03
triamcinolone R03BA06
tribenoside C05CX01
triflusal B01AC18
valrubinic L01BB09
zanamivir J05AH01
zofenopril C09AA15

ATC code changes

donepezil N07AA05 N06DA02
edrecolomab L03AX06 L01XC01
Ginkgo biloba N06BX19 N06DX02
rituximab L01XX21 L01XC02
rivastigmine N07AA06 N06DA03
tacrine N07AA04 N06DA01

Change of level name:
Previous:
Progestogens and estrogens, fixed combinations
New:
Progestogens and estrogens, combinations G03FA
### New DDDs:

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>DDD</th>
<th>Unit</th>
<th>Route of Administration</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>alprostadil</td>
<td>0.25</td>
<td>mg</td>
<td>urethral</td>
<td>G04BE01</td>
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<tr>
<td>anchestim</td>
<td>1.4</td>
<td>mg</td>
<td>P</td>
<td>L03AA12</td>
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<tr>
<td>basiliximab</td>
<td>40</td>
<td>mg</td>
<td>P (course dose)</td>
<td>L04AA09</td>
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<tr>
<td>BCG vaccine</td>
<td>1.8</td>
<td>mg</td>
<td>intra-vesicular</td>
<td>L03AX03</td>
</tr>
<tr>
<td>celecoxib</td>
<td>0.2</td>
<td>g</td>
<td>O</td>
<td>M01AH01</td>
</tr>
<tr>
<td>daclizumab</td>
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<td>g</td>
<td>P (course dose)</td>
<td>L04AA08</td>
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<tr>
<td>desirudin</td>
<td>30</td>
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<td>P</td>
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<td>entacapone</td>
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<td>g</td>
<td>O</td>
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<tr>
<td>filgrastim</td>
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<td>mg</td>
<td>O</td>
<td>J01XX01</td>
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<tr>
<td>immunocyanin</td>
<td>3</td>
<td>mg</td>
<td>intra-vesicular</td>
<td>L03AX10</td>
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<tr>
<td>interferon alfa-2a</td>
<td>2 mill</td>
<td>U</td>
<td>P</td>
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<tr>
<td>interferon alfa-2b</td>
<td>2 mill</td>
<td>U</td>
<td>P</td>
<td>L03AB05</td>
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<tr>
<td>interferon alfa-n1</td>
<td>5 mill</td>
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<td>P</td>
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<tr>
<td>interferon beta-1a</td>
<td>4.3</td>
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<td>P</td>
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<td>interferon beta-1b</td>
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<td>P</td>
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<td>interferon beta natural</td>
<td>33333</td>
<td>U</td>
<td>P</td>
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<td>interferon gamma</td>
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<td>mcg</td>
<td>P</td>
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<td>lenograstim</td>
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<td>P</td>
<td>L03AA10</td>
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<tr>
<td>lentigin</td>
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<td>O, P</td>
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<td>lepirudin</td>
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<td>P</td>
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<td>molgramostim</td>
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<td>P</td>
<td>L03A03</td>
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<td>moxifloxacin</td>
<td>0.4</td>
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<td>O</td>
<td>J01MA14</td>
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<td>nelfinavir</td>
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<td>O</td>
<td>J05AE04</td>
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<td>nevirapine</td>
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<td>g</td>
<td>O</td>
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<td>oprelvekin</td>
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<td>O</td>
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<td>A10BX02</td>
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<td>LSU</td>
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<td>O</td>
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<td>O</td>
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<td>mg</td>
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<td>zofenopril</td>
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* DDD calculated in mg/kg
** DDD refers to salt
### Change of DDDs

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>DDD</th>
<th>Unit</th>
<th>Route of Administration</th>
<th>ATC code</th>
</tr>
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<tr>
<td>cefaclor</td>
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<td>cefatrizine</td>
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<td>O</td>
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<td>P</td>
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<td>cefoperazone</td>
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<td>P</td>
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<td>g</td>
<td>P</td>
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<td>cefuroxime</td>
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<td>g</td>
<td>O</td>
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<td>latamoxef</td>
<td>4</td>
<td>g</td>
<td>P</td>
<td>J01DA18</td>
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</table>
International Nonproprietary Names for Pharmaceutical Substances (INN)

Notice is hereby given that, in accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances, the names given in the list on the following pages are under consideration by the World Health Organization as Proposed International Nonproprietary Names. The inclusion of a name in the lists of Proposed International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

Lists of Proposed (1–73) and Recommended (1–35) International Nonproprietary Names can be found in Cumulative List No. 9, 1996. The statements indicating action and use are based largely on information supplied by the manufacturer. This information is merely meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature, these descriptors will neither be revised nor included in the Cumulative Lists of INNs.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Il est notifié que, conformément aux dispositions de l'article 3 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques les dénominations ci-dessous sont mises à l'étude par l'Organisation mondiale de la Santé en tant que dénominations communes internationales proposées. L'inclusion d'une dénomination dans les listes de DCI proposées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.

On trouvera d'autres listes de Dénominations communes internationales proposées (1–73) et recommandées (1–35) dans la Liste récapitulative No. 9, 1996. Les mentions indiquant les propriétés et les indications des substances sont fondées sur les renseignements communiqués par le fabricant. Elles ne visent qu'à donner une idée de l'utilisation potentielle des nouvelles substances au moment où elles sont l'objet de propositions de DCI. L'OMS n'est pas en mesure de confirmer ces déclarations ni de faire de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations ne figurent pas dans les listes récapitulatives de DCI.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

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

Las listas de Denominaciones Comunes Internacionales Propuestas (1–73) y Recomendadas (1–35) se encuentran reunidas en Cumulative List No. 9, 1996. Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deben incluirse en las listas recapitulativas de DCI.
Proposed International Nonproprietary Names: List 82

Comments on, or formal objections to, the proposed names may be forwarded by any person to the INN Programme of the World Health Organization within four months of the date of their publication in *WHO Drug Information*, i.e., for List 82 Proposed INN not later than 30 June 2000.

Dénominations communes internationales proposées: Liste 82

Des observations ou des objections formelles à l’égard des dénominations proposées peuvent être adressées par toute personne au Programme des Dénominations communes internationales de l’Organisation mondiale de la Santé dans un délai de quatre mois à compter de la date de leur publication dans *WHO Drug Information*, c’est à dire pour la Liste 82 de DCI Proposées le 30 juin 2000 au plus tard.

Denominaciones Comunes Internacionales Propuestas: Lista 82

Cualquier persona puede dirigir observaciones u objeciones respecto de las denominaciones propuestas, al Programa de Denominaciones Comunes Internacionales de la Organización Mundial de la Salud, en un plazo de cuatro meses, contados desde la fecha de su publicación en *WHO Drug Information*, es decir, para la Lista 82 de DCI Propuestas el 30 de junio de 2000 a más tardar.

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

### adalimumabum

**adalimumab**

Immunoglobulin G 1 (human monoclonal D2E7 heavy chain anti-human tumor necrosis factor), disulfide with human monoclonal D2E7k-chain, dimer immunomodulator

### adalimumab

Immunoglobuline G1, anti-(facteur a de nécrose tumorale humain) (chaîne lourde de l’anticorps monoclonal humain D2E7), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal humain D2E7 immunomodulateur

### adalimumab

Immunoglobulina G1 (anti-factor α de necrosis tumoral humano), dímero del disulfuro de la cadena pesada D2E7 monoclonal humana con la cadena κ D2E7 monoclonal humana immunomodulador

### adrogolidum

**adrogolide**

\( (5aR,11bS)-4,5,5a,6,7,11b-hexahydro-2-propylbenzo[f]thieno[2,3-c]quinoline-9,10-diol diacetate (ester) \)

Antiparkinsonian, dopamine D1 receptor agonist

**adrogolide**

Diacéâte de \( (5aR,11bS)-2-propyl-4,5,5a,6,7,11b-hexahydrobenzo[f]thieno[2,3-c]quinoléine-9,10-dyle \)

Antiparkinsonien, agoniste du récepteur D1 de la dopamine

**adrogolida**

Diaceitato (éster) de \( (5aR,11bS)-4,5,5a,6,7,11b-hexahidro-2-propilbenzo=\ [f]tieno[2,3-c]quinolina-9,10-dilo \)

Antiparkinsoniano, agonista del receptor D1 de la dopamina
alemcinalum

8,9-didehydro-N-demethyl-9-deoxo-4''',6,12-trideoxy-6,9-epoxy-N-ethylerythromycin

motilin agonist


agoniste de la motilina

altiniclinum

(-)-5-ethynlnicotine

antiparkinsonian, acetylcholinic receptor agonist

(-)-3-éthynyl-5-[(2S)-1-méthylpyrrolidin-2-yl]pyridine

antiparkinsonien, agoniste du récepteur acétylcholinique

altiniclinica

(-)-5-etinilnicotina

antiparkinsoniano, agonista del receptor de acetilcolina

C_{12}H_{14}N_{2} 179120-92-4
amiglumidum
amiglumide
(R)-4-(2-naphthamido)-N,N-dipentylglutaramic acid
antiulcer agent

amiglumide
acide (4(R))-5-(dipentylamino)-4-[(naphtalen-2-ylcarbonyl)amino]-5-oxopentanoïque
antiulcéreux

amiglumida
(R)-4-(2-naftamido)-N,N-dipentilglutarámico
antiulceroso

C_{26}H_{36}N_{2}O_{4}
119363-62-1

anisperimusum
anisperimus
immunosuppressant

anispérimus
[4-[[[(3R)-3-aminobutyl]amino]butyl]carbamate de
2-[(6-guanidinoheptyl)amino]-2-oxoéthyle
immunosuppresseur

anisperimus
[(6-guanidinohexil)carbamoil]metilo
inmunosupresor

C_{18}H_{39}N_{7}O_{3}
170368-04-4

ataquimastum
ataquimast
1-ethyl-3-(methylamino)-2(1H)-quinoxalinone
tumor necrosis factor antagonist

ataquimast
1-éthyl-3-(méthylamino)quinoxalin-2(1H)-one
antagoniste du facteur de nécrose tumorale

ataquimast
1-etyl-3-(metilamino)-2(1H)-quinoxalinona
antagonista del factor de necrosis tumoral

C_{11}H_{13}N_{3}O
182316-31-0
axitiromum

axitirome ethyl (±)-4’-[α-(p-fluorophenyl)-α,4-dihydroxy-m-tolyl]oxy]-3’,5’-dimethyloxanilate
antihyperlipidaemic

axitirome [(4-[3-[(RS)-4-fluorophényl]hydroxyméthyl]-4-hydroxyphénoxy]-3,5-diméthylphényl]amino]oxoacétate d’éthyle
antihyperlipidémiant

axitiromo (±)-4’-[α-(p-fluorofenil)-α,4-dihidroxi-m-tolil]oxi]-3’,5’-dimetiloxanilato de etilo
antihiperlipémico

C_{25}H_{24}FNO_{6} 156740-57-7

bilastinum

bilastine p-[2-[4-[1-(2-ethoxyethyl)-2-benzimidazolyl]piperidino]ethyl]-α-methylhydratropic acid
histamine-H_{1} receptor antagonist

bilastine acide 2-[4-[2-[4-[2-[1-(2-éthoxyéthyl)-1H-benzimidazol-2-yl]pipéridin-1-yl]éthyl]phényl]-2-méthylpropanoïque
antagoniste des récepteurs H_{1} de l’histamine

bilastina ácido p-[2-[4-[1-(2-etoxietil)-2-bencimidazolil]pipiperdino]etil]-α-metilhidratrópico
antagonista de los receptores H_{1} de la histamina

C_{28}H_{37}N_{3}O_{3} 202189-78-4

binetrakinum

binetrakin interleukin 4 (human)
immunomodulator, interleukin derivative

binétrakine interleukine 4 humaine
immunomodulateur, dérivé d’interleukine

binetrakina interleuquina 4 (humana)
inmunomodulador, derivado de las interleuquinas
bulaquinum

bulaquine  dihydro-3-[1-[[4-[(6-methoxy-8-quinolyl)amino]pentyl]amino]ethylidene]-2(3H)-furanone  antimalarial

bulaquine  3-[(1Z,1-[(4RS)-4-[(6-méthoxyquinoléin-8-yl)amino]pentyl]amino]éthylidène]dihydrofuran-2(3H)-one  antipaludique

bulaquina  dihidro-3-[[4-[(6-metoxi-8-quinolil)amino]pentil]amino]etilideno]-2(3H)-furanona  antipalúdico

C_{21}H_{27}N_{3}O_{3}  223661-25-4

\[
\text{and enantiomer et énantiomère y enantiómero}
\]

cangrelorum

cangrelor  \(N\)-[2-(methylthio)ethyl]-2-[[3,3,3-trifluoropropyl]thio]-5'-adenylic acid, monoanhydride with (dichloromethylene)diphosphonic acid  platelet aggregation inhibitor

cangrélor  monoanhydride dichlorométhylènediphosphonique \(N\)-[2-(méthylsulfanyl)éthyl]-2-[[3,3,3-trifluoropropyl]sulfanyl]-5'-adénylique  antiagrégant plaquettaire

cangrelor  monoanhidrido del ácido \(N\)-[2-(metiltio)etil]-2-[[3,3,3-trifluoropropil]tio]-5'-adenilico con ácido (diclorometileno)difosfónico  inhibidor de la agregación plaquetaria

C_{17}H_{25}Cl_{2}F_{3}N_{5}O_{12}P_{3}S_{2}
**cetuximabum**
cetuximab

immunoglobulin G1 (human-mouse monoclonal C225 γ1-chain anti-human epidermal growth factor receptor), disulfide with human-mouse monoclonal C225 κ-chain, dimer

**immunomodulator**

---

cétuximab

immunoglobuline G1, anti-(récepteur du facteur de croissance humain de l’épiderme) (chaîne γ1 de l’anticorps monoclonal chimérique homme-souris C225), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal chimérique homme-souris C225

**immunomodulateur**

---

cetuximab

inmunoglobulina G 1, anti-(receptor del factor humano de crecimiento de la epidermis)(cadena γ1 del anticuerpo monoclonal quimérico hombre-ratón C225), dímero del disulfuro con la cadena κ del anticuerpo monoclonal quimérico hombre-ratón C225

**inmunomodulador**

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205923-56-4

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**cilomilastum**
cilomilast

cis-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexanecarboxylic acid

**antiasthmatic**

cilomilast

acide cis-4-cyano-4-[3-(cyclopentyloxy)-4-méthoxyphényl]cyclohexanecarboxylique

**antiastmatique**

cilomilast

ácido cis-4-ciano-4-[3-(ciclopentiloxi)-4-metoxifenil]ciclohexanocarboxílico

**antiasmático**

**C₂₀H₂₅NO₄**

153259-65-5

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**conivaptanum**

conivaptan

4''-[(4,5-dihydro-2-methylimidazo[4,5-d][1]benzazepin-6(1H)-yl)carbonyl]-2-biphenylcarboxanilide

**vasopressin V1 and V2 receptor antagonist**

conivaptan


**antagoniste des récepteurs V1 et V2 de la vasopressine**

conivaptán

4''-[(4,5-dihidro-2-metilimidazo[4,5-d][1]benzazepin-6(1H)-ii)carbonil]-2-bifenilcarboxanilida

**antagonista de los receptores V1 y V2 de vasopresina**

**C₃₂H₂₈N₄O₂**

210101-16-9
crobenetinum

(2R,6S)-3-[(2S)-2-(benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocin-10-ol

sodium channel blocker

crobénétine

(2R,6S)-3-[(2S)-2-(benzyloxy)propyl]-6,11,11-triméthyl-1,2,3,4,5,6-hexahydro-2,6-méthano-3-benzazocin-10-ol

antagoniste des canaux sodiques

crobenetina

(2R,6S)-3-[(2S)-2-(benciloxi)propil]-1,2,3,4,5,6-hexahidro-6,11,11-trimetil-2,6-metano-3-benzazocin-10-ol

antagonista del sodio

\( C_{25}H_{33}NO_2 \)

cystinum

cystine

\( L \)-cystine

amino acid

cystine

\( L \)-cystine

acide aminé

cistina

\( L \)-cistina

aminoácido

\( C_6H_{12}N_2O_4S_2 \) 56-89-3

darusentanum

darusentan

\((+)-(S)-2-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-3-methoxy-3,3-diphenylpropionic acid\)

endothelin receptor antagonist

darusentan

\((+)-acide (2S)-2-(4,6-diméthoxyppyrimidin-2-yloxy)-3-méthoxy-3,3-diphenylpropanoïque\)

antagoniste du récepteur de l'endothéline

darusentán

\( (+)-(S)-2-[(4,6-dimetoxi-2-pirimidinil)oxi]-3-metoxi-3,3-difenilpropiónico\)

antagonista del receptor de endotelina

\( C_{22}H_{22}N_2O_6 \) 171714-84-4
**donitriptanum**
donitriptan 1-[[3-(2-aminoethyl)indol-5-yl]oxy]acetyl]-4-(p-cyanophenyl)piperazine 
*antimigraine, serotonin receptor agonist*
donitriptan 1-[2-[[3-(2-aminoéthyl)-1H-indol-5-yl]oxy]acétyl]-4-(4-cyanophényl)pipérazine 
*antimigraineux, agoniste de la sérotonine*
donitriptán 1-[[3-(2-aminoetil)indol-5-il]oxi]acetil]-4-(p-cianofenil)piperazina 
*antimigráñoso, agonista de los receptores de la serotonina*

C\textsubscript{23}H\textsubscript{25}N\textsubscript{5}O\textsubscript{2} 170912-52-4

**doxercalciferolum**
doxercalciferol (5\textsubscript{Z},7\textsubscript{E},22\textsubscript{E})-9,10-secoergosta-5,7,10(19),22-tetraene-1α,3β-diol 
*vitamin D analogue*
doxercalciférol (5\textsubscript{Z},7\textsubscript{E},22\textsubscript{E})-9,10-sécoergosta-5,7,10(19),22-tétraène-1α,3β-diol 
*analogue de la vitamine D*
doxercalciferol (5\textsubscript{Z},7\textsubscript{E},22\textsubscript{E})-9,10-secoergosta-5,7,10(19),22-tetraeno-1α,3β-diol 
*análogo de la vitamina D*

C\textsubscript{28}H\textsubscript{44}O\textsubscript{2} 54573-75-0
emfilerminum  
emfilermine  
emfilermina  
emivirinum  
entecavirum

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emfilermin  
leukemia-inhibiting factor (human)  
growth factor

emfilermine  
acteur d'inhibition leucémique humain  
acteur de croissance

emfilermina  
factor inhibitor de leucemia (humano)  
factor de crecimiento

159075-60-2

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emivirine  
6-benzyl-1-(ethoxymethyl)-5-isopropyluracil  
antiviral

émivirine  
6-benzyl-1-(éthoxyméthyl)-5-(1-méthyléthyl)pyrimidine-2,4(1H,3H)-dione  
antiviral

emivirina  
6-bencil-1-(etoximetil)-5-isopropiluracilo  
antiviral

C_{17}H_{22}N_{2}O_{3}  
149950-60-7

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entecavir  
9-[(1S,3R,4S)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]guanine  
antiviral

entécavir  
2-amino-9-[(1S,3R,4S)-4-hydroxy-3-(hydroxyméthyl)-2-méthyléncyclopentyl]-1,9-dihydro-6H-purin-6-one  
antiviral

entecavir  
9-[(1S,3R,4S)-4-hidroxi-3-(hidroximetil)-2-metilenociclopentil]guanina  
antiviral
epitumomab

epitumomab

C₁₂H₁₅N₅O₃

142217-69-4

epitumomab

epitumomab

HN

N N

N

H₂N

H H

O

H

H OH

CH₂

epitumomab

mouse IgG 1 monoclonal antibody which binds the human muc-1 gene product

antineoplastic

epitumomab

immunoglobuline G2a, anti-(antigène CD20 humain) (chaîne γ2a de l’anticorps monoclonal de souris B1R1), dimère du disulfure avec la chaîne λ de l’anticorps monoclonal de souris B1R1

antineoplásico

epitumomab

immunoglobulina G2a, anti-(antígeno CD20 humano) (cadena γ2a del anticuerpo monoclonal de ratón B1R1), dímero del disulfuro con la cadena λ del anticuerpo monoclonal de ratón B1R1

antineoplásico

epratuzumab

epratuzumab

immunoglobulin G (human-mouse monoclonal IMMU-hLL2 γ-chain anti-human antigen CD22), disulfide with human-mouse monoclonal IMMU-hLL2 κ-chain, dimer

immunomodulator

epratuzumab

immunoglobuline G, anti-(antigène CD22 humain) (chaîne γ de l’anticorps monoclonal de souris IMMU-hLL2 humanisé), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal de souris IMMU-hLL2 humanisé

immunomodulateur

epratuzumab

immunoglobulina G, anti-(antígeno CD22 humano) (cadena γ del anticuerpo monoclonal humanizado de ratón IMMU-hLL2) dímero del disulfuro con la cadena κ del anticuerpo monoclonal humanizado de ratón IMMU-hLL2

immunomodulador

205923-57-5

eptapironum

eptapirone

4-methyl-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-1,2,4-triazine-3,5(2H,4H)-dione

serotonin receptor agonist

eptapirona

4-méthyl-2-[4-[4-(pyrimidin-2-yl)pipérazin-1-yl]butyl]-1,2,4-triazine-3,5(2H,4H)-dione

agoniste de la sérotonine

eptapirone

4-methyl-2-[4-[4-(2-pyrimidinil)-1-piperazinil]butil]-as-triazina-3,5(2H,4H)-diona

agonista de los receptores de la serotonina
escitalopramum

(+)-(S)-1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile

antidepressant

escitalopram

(+)-(1S)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile

antidépresseur

escitalopram

(+)-(S)-1-[3-(dimetilamino)propil]-1-(5-fluorofenil)-5-ftalancarbonitrilo

antidepresivo

C₂₀H₂₁FN₂O 128196-01-0

evernimicinum

O-(1R)-2,3-O-methylene-4-O-(6-methyl-β-resorcyloil)-α-xilopiranósido de

antibacteriano

evernimicina

O-2,3,6-tridesoxi-3-C-metil-4-O-metil-3-nitro-α-L-arabino-hexopiranósido de

antibacteriano
everolimusum
everolimus

\((3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-\{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl\}-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3\textHeptalo[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4\textHeptalo,6\textHeptalo,31\textHeptalo)-pentone

immunosuppressant

évérolimus


immunosupresseur

everolimus

\((3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahidro-9,27-dihidroxi\3H-pirido[2,1-c][1,4]oxazaciclohentriacontina-1,5,11,28,29(4\textHeptalo,6\textHeptalo,31\textHeptalo)-pentona

immunosupresor
**ezlopitantum**

(2S,3S)-2-(diphenylmethyl)-3-[(5-isopropyl-2-methoxybenzyl)amino]quinuclidine

* tachykinin receptor antagonist

**ezlopitant**

(2S,3S)-2-(diphenylmethyl)-N-[2-methoxy-5-(1-methyllethyl)benzyl]-1-azabicyclo[2.2.2]octan-3-amine

* antagoniste de récepteurs de la tachykinine

**ezlopitant**

(2S,3S)-2-(difenilmetil)-3-[(5-isopropil-2-metoxibencil)amino]quinuclidina

* antagonista del receptor de taquiquinina

**fiduxosinum**


* α₁a-adrenoreceptor antagonist

**fiduxosin**


* antagoniste α₁a-adrénergique

**fiduxosina**


* antagonista de los receptores α₁a-adrenérgicos
figopitantum

figopitant

$(S)$-$N$-[bis(3,5-trifluoromethyl)phenethyl]-4-(cyclopropylmethyl)-$N$-methyl-$\alpha$-phenyl-1-piperazineacetamide  
neurokinin NK-1 receptor antagonist

figopitant

$(2S)$-$N$-[2-[3,5-bis(trifluoromethyl)phenyl]ethyl]-2-[4-(cyclopropylmethyl)-N-methyl-2-phenylacetamide  
antagoniste du récepteur de la neurokinine NK-1

figopitant

$(S)$-$N$-[bis(3,5-trifluoromethyl)fenetil]-4-(ciclopropilmetil)-$N$-metil-$\alpha$-fenil-1-piperazaacetamida  
antagonista del receptor NK-1 de la neuroquinina

implitapidum

implitapide

$(\alpha S)$-$\alpha$-[$\alpha$-(2,4-dimethyl-9H-pyrido[2,3-b]indol-9-yl)-p-tolyl]-N-[(\alpha R)$-$\alpha$-(hidroximetil)bencil)ciclopentaneacetamida  
antihyperlipidaemic

implitapide

$(2S)$-2-cyclopentyl-2-[4-[(2,4-diméthyl-9H-pyrido[2,3-b]indol-9-yl)méthyl]phényl]-N-[(1R)-2-hydroxy-1-phényléthyl]acétamide  
antihyperlipidéant

implitapida

$(\alpha S)$-$\alpha$-[$\alpha$-(2,4-dimetil-9H-pirido[2,3-b]indol-9-il)-p-tolil]-N-[(\alpha R)$-$\alpha$-(hidroximetil)bencil)ciclopentanoacetamida  
antihiperlipémico

C$_{30}$H$_{29}$N$_{5}$O$_{4}$S  208993-54-8

C$_{27}$H$_{31}$F$_{6}$N$_{3}$O  

C$_{35}$H$_{37}$N$_{3}$O$_{2}$  177469-96-4
**irampanelum**

**irampanel**  
5-[o-[2-(dimethylamino)ethoxy]phenyl]-3-phenyl-1,2,4-oxadiazole
**AMPA-antagonist**

**irampanel**  
N,N-diméthyl-2-[2-(3-phényl-1,2,4-oxadiazol-5-yl)phénoxy]éthanamine
**antagoniste d’AMPA**

**irampanel**  
5-[o-[2-(dimetilamino)etoxi]fenil]-3-fenil-1,2,4-oxadiazol
**antagonista del AMPA**

\[\text{C}_{18}\text{H}_{19}\text{N}_{3}\text{O}_{2}\] 206260-33-5

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**irofulvenum**

**irofulven**  
(R)-6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethylspiro[cyclopropane-1,5'-[5\text{H}]inden]-7'(6'H)-one
**antineoplastic**

**irofulvène**  
(6 \(R\))-6'-hydroxy-3'-(hydroxyméthyl)-2',4',6'-triméthylspiro[cyclopropane-1,5'-[5\text{H}]indén]-7'(6\text{H}')-one
**antinéoplasique**

**irofulveno**  
(R)-6'-hidroxi-3'-(hidroximetil)-2',4',6'-trimetilspiro[ciclopropano-1,5'-[5\text{H}]inden]-7'(6'\text{H}')-ona
**antineoplásico**

\[\text{C}_{15}\text{H}_{18}\text{O}_{3}\] 158440-71-2

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**itriglumidum**

*itriglumide*  
(R)-2’-(8-azaspiro[4.5]dec-8-ylcarbonyl)-4’,6’-dimethyl-3-(1-naphthyl)glutaric acid  
*antiulcer agent*

*itriglumide*  
acide (3R)-5-[[2-(8-azaspiro[4.5]dec-8-ylcarbonyl)-4,6-diméthylphényl]amino]-3-(naphtalén-1-yl)-5-oxopentanoïque  
*antiulcéreux*

*itriglumida*  
ácido (R)-2’-(8-azaspiro[4.5]dec-8-ilcarbonil)-4’,6’-dimetil-3-(1-naftil)glutaranilico  
*antiulceroso*

\[\text{C}_{33}\text{H}_{38}\text{N}_2\text{O}_4\]  
201605-51-8

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**laniceminum**

*lanicemine*  
(+)-2-[(S)-β-aminophenethyl]pyridine  
*NMDA receptor antagonist*

*lanicémine*  
(+)-(1S)-1-phényl-2-(pyridin-2-yl)éthanamine  
*antagoniste des récepteurs du NMDA*

*lanicemina*  
(+)-2-[(S)-β-aminofenetil]piridina  
*antagonista de los receptores de NMDA*

\[\text{C}_{13}\text{H}_9\text{N}_2\]  
153322-05-5
lusaperidonum
lusaperidone
3-[2-(3,4-dihydrobenzofuro[3,2-c]pyridin-2(1H)-yl)ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one
antidepressant
C_{22}H_{21}N_{3}O_{2}  214548-46-6

metreleptininum
metreleptin
N-methionylleptin (human)
antihyperlipidaemic
C_{714}H_{1167}N_{191}O_{221}S_{6}  186018-45-1

mitumomabum
mitumomab
immunoglobulin G2b (mouse monoclonal BEC2 γ2b-chain anti-GD3 ganglioside), disulfide with mouse monoclonal BEC2 κ-chain, dimer
immunomodulator
216503-58-1
**motexafinum**

motexafin  
9,10-diethyl-20,21-bis[2-[(2-methoxyethoxy)ethoxy]ethoxy]-4,15-dimethyl-8,11-imino-6,3:13,16-dinitrilo-1,18-benzodiazacycloeicosine-5,14-dipropanol  
*antineoplastic*

motéxafine  
*antineoplasique*

motexafina  
9,10-dietil-20,21-bis[2-[(2-metoxietoxi)etoxi]etoxi]-4,15-dimetil-8,11-imino-6,3:13,16-dinitrilo-1,18-benzodiazacicloeicosina-5,14-dipropanol  
*antineoplásico*

**C₅₂H₇₂GdN₅O₁₄**

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**nebostinelim**

nebostinel  
(S)-4-amino-N-(4,4-dimethylcyclohexyl)glutaramic acid  
*NMDA receptor antagonist*

nébostinel  
acide (4S)-4-amino-5-[(4,4-diméthylcyclohexyl)amino]-5-oxopentanoïque  
*antagoniste des récepteurs du NMDA*

nebostinel  
ácido (S)-4-amino-N-(4,4-dimetilciclohexil)glutarámico  
*antagonista de los receptores de NMDA*

**C₁₃H₂₄N₂O₃**  
163000-63-3
onerceptum

glycoprotein TNF-BP (tumor necrosis factor-binding protein) (human disulfide variant 1) immunomodulator

onercept

20-180-récepteur 1 humain du facteur de nécrose tumorale, protéine glycosylée (partie du domaine extracellulaire) immunomodulateur

onercept

glicoproteína TNF-BP (proteína de unión al factor de necrosis tumoral)(disulfuro de la variante 1 humana) immunomodulador

C_{753}H_{1156}N_{228}O_{247}S_{25} 199685-57-9

pegvisomantum


pegvisomant


pegvisomant

**perflexanum**
perflexane
tetradecafluorohexane
ultrasound contrast agent

**perflexane**
tétradécafluorohexane
produit de contraste pour des analyses ultrasoniques

**perflexano**
tetradecaffluorohexano
medio de contraste para análisis por ultrasonido

\[ C_{6}F_{14} \quad 355-42-0 \]

**perflutrenum**
perflutren
octafluoropropane
ultrasound contrast agent

**perflutren**
octafluoropropane
produit de contraste pour des analyses ultrasoniques

**perflutreno**
octafluoropropano
medio de contraste para análisis por ultrasonido

\[ C_{3}F_{8} \quad 76-19-7 \]

**pinokalantum**
pinokalant
(±)-3,4-dihydro-6,7-dimethoxy-α-phenyl-N,N-bis(2,3,4-trimethoxyphenethyl)-1-isoquinolineacetamide
ion channel blocker

**pinokalant**
(2RS)-2-(6,7-diméthoxy-3,4-dihydroisooquinoléin-1-yl)-2-phényl-N,N-bis[2-(2,3,4-triméthoxyphényl)éthyl]acétamide
antagoniste des canaux ioniques

**pinokalant**
(±)-3,4-dihidro-6,7-dimetoxi-α-fenil-N,N-bis(2,3,4-trimetoxifenetil)-1-isoquinolinacetamida
bloqueante de los canales de iones

* pegylation sites
* sites de pégylation
* posiciones de pegilación
**posaconazolum**

4-[p-[4-[p-[[3(R),(5,R)]-5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furyl]methoxy][phenyl]-1-piperazinyl][phenyl]-1-[(1S,2S)-1-ethyl-2-hydroxypropyl]-D²-1,2,4-triazolin-5-one

antifungal

**posaconazole**

4-[4-[4-[4-[4-[3(R),(5,R)]-5-(2,4-difluorophenyl)-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furyl]methoxy][phenyl]-1-piperazinyl][phenyl]-2-[(1S,2S)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one

antifongique

**posaconazol**

4-[p-[4-[p-[[3(R),(5,R)]-5-(2,4-difluorofenil)tetrahidro-5-(1H-1,2,4-triazol-1-ilmetil)-3-furil]metoxi][fenil]-1-piperazinil][fenil]-1-[(1S,2S)-1-etil-2-hidroxipropil]-D²-1,2,4-triazolin-5-ona

antifúngico

**prinomastatum**

(S)-2,2-dimethyl-4-[p-(4-pyridyloxy)phenyl]sulfonyl]-3-thiomorpholinecarboxyhydroxamio acid

matrix metalloproteinase inhibitor

**prinomastat**

(3S)-N-hydroxy-2,2-diméthyl-4-[4-(pyridin-4-yloxy)phényl]sulfonyl]-thiomorpholine-3-carboxamide

inhibiteur de la métalloprotéinase de la matrice

**prinomastat**

ácido (S)-2,2-dimetil-4-[p-(4-piridiloxi)fenil]sulfonil]-3-tiomerfolinacarbohidroxámico

inhibidor de la metaloproteinasa de matriz
pumafentrinum

pumafentrine

(\(-\))-p\-[(4aR\(^*\),10bS\(^*\))-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-disopropylbenzamide

phosphodiesterase inhibitor

pumafentrine

(\(-\))-4\-[(4aR\(^*\),10bS\(^*\))-9-éthoxy-8-méthoxy-2-méthyl-1,2,3,4,4a,10b-hexahydrobenzo[c][1,6]naphthyridin-6-yl]-N,N-bis(1-méthyléthyl)benzamide

inhibiteur de la phosphodiestérase

pumafentrina

(\(-\))-p\-[(4aR\(^*\),10bS\(^*\))-9-etoxi-1,2,3,4,4a,10b-hexahidro-8-metoxi-2-metilbenzo[c][1,6]naftiridina-6-il]-N,N-diisopropilbenzamida

inhibidor de la fosfodiesterasa

C\(_{29}\)H\(_{39}\)N\(_3\)O\(_3\) 207993-12-2

radolmidinum

radolmidine

3\-{(imidazol-4-ylmethyl)}-5-indanol

\(\alpha_2\)-adrenoreceptor agonist

radolmidine

(3RS)-3\-{[1\-H-imidazol-4-yl]méthyl]-2,3-dihydro-1\-H-indén-5-ol}

agoniste \(\alpha_2\)-adrénergique

radolmidina

3\-{(imidazol-4-ilmetil)}-5-indanol

agonista de los receptores \(\alpha_2\)-adrenérgicos

C\(_{13}\)H\(_8\)N\(_2\)O 189353-31-9

or enantiomer
ou énantiomère
y enantiómero
relovacaptanum
relovacaptan
relovacaptán

(2S)-1-[(2R,3S)-5-chloro-3-(o-chlorophenyl)-1-[(3,4-dimethoxyphenyl)=sulfonyl]-3-hydroxy-2-indolyl]carbonyl]-2-pyrrolidinacarboxamide

vasopressin V1 receptor antagonist
antagoniste du récepteur V1 de la vasopression
antagonista del receptor V1 de la vasopresina

C_{28}H_{27}Cl_{2}N_{3}O_{7}S_{1} 150375-75-0

repiferminum
repifermin
répifermine
repifermina

33-172-keratinocyte growth factor 2 (human)
fibroblast growth factor

33-172-facteur 2 humain de croissance du kératinocyte
facteur de croissance des fibroblastes

33-172-factor 2 de crecimiento de queratinocitos (humano)
factor de crecimiento de fibroblastos

C_{723}H_{1131}N_{209}O_{204}S_{5} 219527-63-6

resiquimodum
resiquimod
résiquimod
resiquimod

4-amino-2-(ethoxymethyl)-α, α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol
immunomodulator

1-[4-amino-2-(éthoxyméthyl)-1H-imidazo[4,5-c]quinoléin-1-yl]-2-méthylpropan-2-ol
immunomodulateur

4-amino-2-(etoximetil)-α, α-dimetil-1H-imidazo[4,5-c]quinolina-1-etanol
immunomodulador
risarestatum
risarestat (±)-5-[3-ethoxy-4-(pentyloxy)phenyl]-2,4-thiazolidinedione
aldose reductase inhibitor
risarestat (5RS)-5-[3-éthoxy-4-(pentyl oxy)phényl]thiazolidine-2,4-dione
inhibiteur de l’aldose réductase
risarestat (±)-5-[3-etoxi-4-(pentiloxi)fenil]-2,4-tiazolidinadiona
inhibidor de la reductasa de aldosas
C_{17}H_{22}N_{4}O_{2} 144875-48-9

rubitecanum
rubitecan 9-nitrocamptothecin
antineoplastic
rubitécan (4S)-4-éthyl-4-hydroxy-10-nitro-1,12-dihydro-14H-pyran[3',4':6,7]=
indolizino[1,2-b]quinoléine-3,14(4H)-dione
antineoplásico
rubitecán 9-nitrocamptotecina
antineoplásico
C_{20}H_{15}N_{3}O_{6} 91421-42-0
**sulamserodum**

sulamserod  
\[N-[2-[4-[2-[(8-amino-7-chloro-1,4-benzodioxan-5-yl)carbonyl]ethyl]piperidino]-
\text{ethyl}][\text{methanesulfonamide]}

*serotonin receptor antagonist*

sulamsérod  
\[N-[2-[4-[3-(8-amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-
3-oxopropyl]pipéridin-1-yl]éthyl][méthanesulfonamide]  
*antagoniste de la sérotonine*

sulamserod  
\[N-[2-[4-[2-[(8-amino-7-cloro-1,4-benzodioxan-5-il)carbonil]etil]piperidino]-
etil][metanosulfonamida]  
*antagonista de los receptores de la serotonina*

\[C_{19}H_{28}ClN_{3}O_{5}S\]

![Chemical Structure of Sulamserodum](image)

---

**tanomastatum**

tanomastat  
\[(S)-3-[(4'-chloro-4-biphenylyl)carbonyl]-2-[(phenylthio)methyl]propionic acid]  
*matrix metalloproteinase inhibitor*

tanomastat  
\[acide (2S)-4-(4'-chlorobiphényl-4-yl)-4-oxo-2-[(phénylsulfanyl)méthyl]=
butanoïque  
*inhibiteur de la métalloprotéinase de la matrice*

tanomastat  
\[ácido (2S)-4-(4'-clorobifenil-4-il)-4-oxo-2-[(fenilsulfanilo)métil]butanoico]  
*inhibidor de la metaloproteinasa de matriz*

\[C_{23}H_{19}ClO_{3}S\]  179545-77-8

![Chemical Structure of Tanomastatum](image)
tebipenem  
\[N\{2\{4\{2\[(8\text{-amino-7-chloro-1,4-benzodioxan-5-yl})\text{carbonyl]}\text{ethyl}]\text{piperidino}\}=\text{ethyl}]\text{methanesulfonamide}\]  
\textit{antibiotic}

tébipénem  
\((+)-(4R,5S,6S)-3\{[1\{4,5\text{-dihydrothiazol-2-yl}]\text{azétidin-3-yl}]\text{sulfanyl}]\{6\{[(1R)-1-hydroxyéthyl]\{4\text{-méthyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ène-2-carboxylate de [(2,2-diméthylpropanoyl]oxy]méthyle}\]\textit{antibiotique}\]

tebipenem  
\[2\text{-pivalato y (4R,5S,6S)-6\{[(1R)-1-hidroxietil]\{4-métil-7-oxo-3\{[1\{2-tiazolin-2-il-3-azetidinil]tio\]-1-azabiciclo[3.2.0]hept-2-eno-2-carboxilato de metíleno}\]\textit{antibiótico}\]

\[\text{C}_{22}\text{H}_{31}\text{N}_{3}\text{O}_{6}\text{S}_{2}\quad161715-24-8\]

![Chemical Structure of tebipenem]

<table>
<thead>
<tr>
<th>Proprietary Name</th>
<th>Scientific Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>tenofovirum</td>
<td>[([(R)-2{6\text{-amino-9H-purin-9-yl}]\text{-1-methylethoxy}]\text{methyl}]\text{phosphonic acid}</td>
</tr>
<tr>
<td>tenofovir</td>
<td>\textit{antiviral}</td>
</tr>
<tr>
<td>ténofovir</td>
<td>acide [([(1R)-2{6\text{-amino-9H-purin-9-yl}]\text{-1-méthyléthoxy}]\text{méthyl}]\text{phosphonique}</td>
</tr>
<tr>
<td>tenofovir</td>
<td>\textit{antiviral}</td>
</tr>
<tr>
<td>tenofovir</td>
<td>[([(R)-2{6\text{-amino-9H-purin-9-il}]\text{-1-metiletoxi}]\text{metil}]\text{fosfónico}</td>
</tr>
<tr>
<td>C_{9}H_{14}N_{5}O_{4}P H_{2}O</td>
<td>147127-20-6</td>
</tr>
</tbody>
</table>

![Chemical Structure of tenofovir]
**tiplimotidum**

**tiplimotide**


*immunomodulator*

**tiplimotide**


*immunomodulateur*

**tiplimotida**


*inmunomodulador*

\[\text{C}_{87}\text{H}_{143}\text{N}_{25}\text{O}_{20}\]

178823-49-9

\[\text{D- Ala — Lys — Pro — Val — Val — His — Leu — Phe — Ala — Asn —}\]

Ile — Val — Thr — Pro — Arg — Thr — Pro — NH\(_2\)

---

**valrocemidum**

**valrocemide**

\[\text{N-(carbamoylmethyl)-2-propylvaleramide}\]

*antiépileptic*

**valrocémide**

\[\text{N-(2-amino-2-oxoéthyl)-2-propylpentanamide}\]

*antiépileptique*

**valrocemida**

\[\text{N-(carbamoilmetil)-2-propilvaleramida}\]

*antiepiléptico*

\[\text{C}_{10}\text{H}_{20}\text{N}_{2}\text{O}_{2}\]

92262-58-3

---

**vardenafilum**

**vardenafil**

\[\text{1-[[3-(3,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f]-triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethylpiperazine}\]

*vasodilatator*

**vardénafil**

\[\text{2-[[2-éthoxy-5-[[4-éthylpipérazin-1-yl]sulfoneyl]-5-méthyl-7-propylimidazo[5,1-f][1,2,4]triazin-4(3\text{H})-one}\]

*vasodilatateur*

**vardenafil**

\[\text{1-[[3-(3,4-dihidro-5-metil-4-oxo-7-propilimidazo[5,1-f]-as-triazin-2-il)-4-etoxifenil]sulfonil]-4-etilpiperazina}\]

*vasodilatador*

\[\text{C}_{23}\text{H}_{32}\text{N}_{6}\text{O}_{4}\text{S}\]

224785-90-4
vofopitantum

vofopitant

(2S,3S)-3-[[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]amino]-2-phenylpiperidine

antiemetic, tachykinin receptor antagonist

vofopitant

(2S,3S)-N-[2-méthoxy-5-[5-(trifluorométhyl)-1H-tétrazol-1-yl]benzyl]-2-phénylpipéridin-3-amine

antiémétique, antagoniste de récepteurs de la tachykinine

vofopitant

(2S,3S)-3-[[2-metoxi-5-[5-(trifluorometil)-1H-tetrazol-1-yl]bencil]amino]-2-fenilpiperidina

antiemético, antagonista del receptor de taquiquinina

C_{21}H_{23}F_{3}N_{6}O
168266-90-8
Names for radicals and groups

Some substances for which an international nonproprietary name has been established may be used in the form of salts or esters. The radicals or groups involved maybe of complex composition and it is then inconvenient to refer to them in systematic chemical nomenclature. Consequently, shorter non proprietary names for some radicals and groups have been devised or selected, and they are suggested for use with the proposed and recommended international nonproprietary names.

Dénominations applicables aux radicaux et groupes

Certaines substances pour lesquelles une dénomination commune internationales a été établie sont parfois utilisées sous forme de sels ou d'esters. Les radicaux ou groupes correspondants sont alors quelquefois si complexes qu'il est malcommode de les désigner conformément à la nomenclature chimique systématique. Des dénominations communes abrégées ont donc été formées ou choisies pour certains d’entre eux et ils est suggéré de les employer avec les dénominations communes internationales proposées et recommandées.

Denominaciones para radicales y grupos

Ciertas sustancias para las cuales hay establecida una denominación común pueden usarse en forma de sales o de ésteres. Los radicales o grupos correspondientes pueden llegar a tener una composición tan compleja que resulte incómodo referirse a ellos mediante la nomenclatura química sistemática. Las siguientes denominaciones comunes abreviadas han sido ideadas o elegidas para algunos de estos radicales y grupos y se sugiere que se empleen con las denominaciones comunes internacionales propuestas y recomendadas.

soproxilum
soproxil [(isopropoxycarbonyl)oxy]methyl
soproxil [[(1-méthyléthoxy)carbonyl]oxy]méthyle
soproxil [(isopropoxicarbonil)oxi]metil

\[
\text{C}_6\text{H}_9\text{O}_3
\]

\[
\text{H}_3\text{C} \quad \text{O} \quad \text{CH}_2
\]

\[
\text{CH}_3 \quad \text{O} \quad \text{O} \quad \text{CH}_2
\]
AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Proposed International Nonproprietary Names (Prop. INN): List 76
Dénominations communes internationales proposées (DCI Prop.): Liste 76
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 76
(WHO Drug Information, Vol. 10, No. 4, 1996)

p. 213 opratonii ioididum
opratonium iodide replace the CAS registry number by the following:
iiodure d’opratonium remplacer le numéro dans le registre du CAS par:
iioduro de opratonio sustitúyase el número de registro del CAS por:
210419-36-6

Proposed International Nonproprietary Names (Prop. INN): List 80
Dénominations communes internationales proposées (DCI Prop.): Liste 80
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 80
(WHO Drug Information, Vol. 12, No. 4, 1998)

p. 270 delete/supprimer/suprimase insert/insérer/insértese
olmesartanum olmesartanum medoxomilum
olmesartan olmesartan medoxomil
olmésartan olmésartan médoxomil
olmesartán olmesartán medoxmilo

Proposed International Nonproprietary Names (Prop. INN): List 81
Dénominations communes internationales proposées (DCI Prop.): Liste 81
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 81
(WHO Drug Information, Vol. 13, No. 2, 1999)

p. 123 rasburicasum
rasburicase add the following CAS registry number:
rasburicase insérer le numéro dans le registre du CAS suivant:
rasburicasa insértese el número de registro del CAS siguiente:
134774-45-1
Procedure and Guiding Principles / Procédure et Directives / Procedimientos y principios generales

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

Les textes de la *Procédure à suivre en vue de 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* ont été publiés avec la liste 81 des DCI proposées et seront, à nouveau, publiés avec la prochaine liste.

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