

WHO Drug Information

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Rational Use of Drugs

Prescribing information in 26 countries

Pharmaceutical products approved for marketing are generally accompanied by information targeted to health care prescribers and patients. The International Comparative Study on Drug Information (ICSODI) Collaborative Group has recently published an article in the *European Journal of Clinical Pharmacology* which documents the variability of written drug information in and within countries concerning the indications, side effects and cautions of three selected drugs: ciprofloxacin, fluoxetine and nifedipine. An original method to measure the degree of information agreement among different written materials, such as summaries of product characteristics, package inserts and data sheets, and a widely accepted reference text was developed (1).

Published studies addressing drug information in general (2–5) and readability of patient information materials (6–8) are available, but very little specifically address the issue of documenting differences in key aspects of drug information among different countries for the same drugs (9).

The selected drugs figured among the top thirty in terms of global sales in 2000 (10), and covered

three therapeutic areas of high worldwide relevance in terms of mortality and morbidity (11).

A total of 483 written materials were obtained from 26 countries and analysed. Four variables: indications, dosage range in adults, side effects, and cautions were selected and a checklist of items was created using the British National Formulary as a reference text (12). The BNF was chosen because it is a complete, independent, and practice-oriented source of information and is widely used by professionals around the world, being easy to obtain and inexpensive.

Materials collected from each country, drug, and variable were compared with a checklist (see page 146). An indicator for the proportion of agreement was developed. The indicator was called “degree of information agreement” and was based on indications, side effects, and cautions for each country and drug. The proportion of checklist items found in the materials was calculated against the total number of relevant checklist items. The mean and confidence interval for the proportions were then calculated.

The same checklist and methodological approach used in the inter-country evaluation was applied to comparators among materials collected from each individual country.

Baseline characteristics of evaluated materials (26 countries)

		ciprofloxacin (500 mg)	fluoxetine (20 mg)	nifedipine (10–20 mg)
Companies (No.)		5 different (Bayer in 22 countries)	6 different (Ely Lilly in 21 countries)	7 different (Bayer in 20 countries)
Year of marketing authorization	Range Median	1987–1999 1994	1987–2000 1992	1976–1999 1991
Approved material	Yes No	14 12	18 8	18 8

**BNF-derived checklist for assessing agreement
of drug information material**

	ciprofloxacin (500 mg)	fluoxetine (20 mg)	nifedipine (20 mg)
Indications	respiratory and urinary tract infections, chronic prostatitis, gonorrhoea, pseudomonas lower respiratory tract infection in cystic fibrosis, gastrointestinal infection (including typhoid fever), septicaemia caused by sensitive organisms, surgical prophylaxis, corneal ulcers, skin and soft-tissue infections	depressive illness, bulimia nervosa, obsessive-compulsive disorder, premenstrual dysphoric disorder	prophylaxis of angina, hypertension, Raynaud phenomenon
Dose (oral, daily, adults)	500–1500 mg	20–60 mg	15–80 mg
Side effects	nausea, diarrhoea, vomiting, abdominal pain, jaundice, hepatitis with necrosis, headache, restlessness, Stevens Johnson Syndrome, haemorrhagic bullae, toxic epidermal necrolysis, increase in blood urea and creatinine, hepatic dysfunction (increased serum concentrations of AST and ALT), renal failure, convulsions, hypersensitivity reactions, tendon inflammation and damage	hypersensitivity reactions (angioedema, urticaria, anaphylaxis, pharyngitis, pulmonary inflammation or fibrosis, arthralgia, myalgia, serum sickness), nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, constipation, sexual dysfunction, sweating, dry mouth, tremor, nervousness, insomnia, anxiety, headache, lightheadedness, dizziness, suicidal ideation, anorexia with weight loss, movement disorders and dyskinesia, fever, anaemia, convulsion, neuroleptic malignant syndrome-like event, aplastic cerebrovascular accident, eosinophilic pneumonia, gastrointestinal haemorrhage, pancreatitis, pancytopenia, thrombocytopenia, thrombocytopenic purpura, violent behaviour	headache, flushing, dizziness, gravitational edema, exaggerated fall in blood pressure and reflex tachycardia which may lead to myocardial ischaemia, or cerebrovascular ischaemia (short-acting preparation), nausea
Cautions	pregnancy, breast-feeding, children and adolescents, photosensitivity, renal impairment, history of epilepsy, avoid excessive alkalinity of urine, G6PD deficiency, myasthenia gravis	diabetes mellitus, epilepsy, hepatic and renal impairment, pregnancy, breast-feeding, concurrent electroconvulsive therapy, cardiac disease, history of bleeding disorders, skilled tasks (impairment), avoid abrupt withdrawal, history of mania, angle closure glaucoma	advanced aortic stenosis, myocardial infarction within 1 month, unstable or acute attacks of angina, porphyria, severe hypotension, pregnancy, heart failure, breast-feeding, hepatic impairment, diabetes mellitus, ischaemic pain, avoid grapefruit juice

A comparison was made between the information stated in the BNF and that found in the materials collected. Out of 26 countries, 11 had information that matched BNF indications for nifedipine. Only materials from Colombia and the UK listed all the indications included in the BNF for ciprofloxacin, and those from Canada, Estonia and the UK for fluoxetine. Concerning ciprofloxacin, materials from 3 countries are in disagreement with the dose range recommended by the BNF. This disagreement involved a total of 7 countries for nifedipine and 9 for fluoxetine, i.e. over one-third of the sample. None of the materials from the various countries reported all major side effects listed in the BNF for ciprofloxacin and fluoxetine.

Concerning nifedipine, only materials from Spain were found to report all the BNF side effects, while materials from Colombia did not report any of the 7 major side effects included in the BNF. Again, none of the materials from any of the countries report all the cautions included in the BNF. The findings of this study include extremes such as the presence of 1 caution statement out of the 19 listed in the BNF for ciprofloxacin in the Philippines, 1 out of 11 for fluoxetine in Argentina, and 3 out of 12 for nifedipine in Mozambique and Poland.

What did the analysis show?

Looking at inter-country comparisons, the degree of information agreement is surprisingly low for drugs that are routinely used in large numbers of patients. The disparity of dose ranges recommended by the different sources is especially surprising. Theoretically, prescribing information is based on the assessment of clinical studies and post marketing surveillance activities. In the majority of the cases studied, the materials collected were related to products of the same mother company thus leading to the assumption that the same basic facts should have been used to make the decisions concerning indications, dosage, side effects, and cautions. However, the results show that prescribers and patients are recommended substantially different things in different countries and this may be due to the fact that not all national authorities can conduct a full and systematic assessment of available worldwide data concerning clinical studies and drug monitoring data before approving prescribing information materials.

If intra-country comparisons are examined, the picture becomes even more difficult to understand: why should products have different

indications, dosages, side effects and cautions simply because they have a different brand name?

While a plausible explanation cannot be offered for the differences found, it is possible that the implications at national level can be serious for patients and for those engaged in activities aimed at ensuring rational drug use. These implications can also involve communication problems between prescribers, regulatory authorities, companies, and patients. At the international level, there can be serious implications for travellers, or for health workers comparing drug utilization or developing therapeutic guidelines.

In the case of safety information, this was often presented as a list with no frequency indications or any specific guidance for prescribers or patients. Patients presented with such a list of side effects may be reluctant to continue taking a drug. The conclusion is that a list lacking practical guidance is not particularly useful to prescribers or patients. It is urgent for companies and regulatory authorities to understand that correctly presented safety information will assist in decision-making and can speed up identification of adverse reactions.

Responsibility for approving drug information materials lies with national regulatory authorities. Their task is difficult, especially when resources are limited and companies submit different materials in different countries. An effort should be made to identify sources of independent drug information that can be used as a complement to documentation submitted for approval thereby removing contradictory statements on drug information materials that have no reason to be different. Further training and continued education aimed at drug regulatory officials could play a role. Finally, measures to harmonize information materials at the national level, such as requiring the use of core information for pharmaceutically-equivalent products, should be implemented.

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Safety and Efficacy Issues

Virologic non-response in HIV drugs

A high rate of early virologic non-response has been observed in a clinical study of therapy-naïve adults receiving once-daily three-drug combination therapy with lamivudine (EpiVir®), abacavir (Ziagen®) and tenofovir (Viread™) (1).

Based on these results:

- Abacavir and lamivudine in combination with tenofovir should not be used as a triple antiretroviral therapy when considering a new treatment regimen for naïve or pre-treated patients;
- Any patient currently controlled on therapy with this combination should be closely monitored and considered for modification of therapy; and
- Any usage of this triple combination with other antiretroviral agents should be closely monitored for signs of treatment failure.

ESS30009 is a randomized, open-label, multi-centre study on the safety and efficacy of efavirenz (EFV) versus tenofovir (TDF) when administered in combination with an investigational abacavir(ABC)/lamivudine (3TC) fixed-dose combination tablet as a once-daily regimen in antiretroviral-naïve HIV-1 infected adults.

Shortly after initiation of this study the sponsor, GlaxoSmithKline, received reports from investigators of poor efficacy in patients receiving TDF+3TC+ABC. An urgent, unplanned interim analysis

was conducted to assess virologic non-response. Results are shown in the table below. The precise nature of any interaction leading to non-response in this study is not known. Preliminary genotypes of viral isolates from 14 patients with non-response taking the TDF+3TC+ABC regimen have shown all 14 isolates had the M184V mutation in HIV reverse transcriptase. In addition, 8 of the 14 (57%) isolates also had the K65R mutation.

On review of these results, GSK promptly informed all participating clinical investigators and terminated the TDF+3TC+ABC arm in this study. Clinical investigators are working with patients to change therapy based on genotype and clinical judgement. The once daily EFV+3TC+ABC arm performed well and continues unchanged in this clinical study.

In addition to study ESS30009, a pilot study (2) has provided data in 20 patients receiving TDF+3TC+ ABC once daily for initial therapy. A high rate of virologic non-response was also documented.

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3. Informative Note 2003/09. Spanish medicines Agency, 31 July 2003 <http://www.agemed.es>.

	Number (%) of patients meeting the definition of virologic non-response	
	TDF + 3TC + ABC	EFV + 3TC + ABC
HIV-1 RNA data for subjects on therapy for > or equal to 8 weeks	50 / 102 (49%)	5 / 92 (5%)
HIV-1 RNA data for subjects on therapy for > or equal to 12 weeks	30 / 63 (48%)	3 / 62 (5%)

Hyponatraemia with SSRIs

The Australian Adverse Reactions Advisory Committee (ADRAC) has received a total of 311 reports of hyponatraemia involving serotonin selective reuptake inhibitors (SSRIs) and venlafaxine. In 67 of these reports, it was indicated that the patient had the syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) although serum and/or urine osmolality results were not included in every case (1). As a group, the SSRIs account for about one-quarter of all reports of hyponatraemia received by ADRAC, and are second to diuretics as the group most commonly associated with hyponatraemia.

Reports of hyponatraemia with SSRIs and venlafaxine

Drug	Total reports	Reports of hyponatraemia
Citalopram	388	35
Fluoxetine	1148	50
Fluvoxamine	142	3
Paroxetine	1587	46
Sertraline	4503	130
Venlafaxine	695	47

In more than two-thirds of the 311 reports, the SSRI was the only suspected drug and three-quarters of the reports involved females. A small proportion (14%) identified concurrent use of a diuretic. The median patient age was 77 years (range 13 to 99); about 85% were older than 60 years. Onset was usually within the first month of treatment. In many of the reports hyponatraemia was the sole abnormality reported, with the median serum sodium nadir at 120 (range 113 to 133) mmol/L. Other reports listed neuropsychological symptoms such as confusion, convulsions, fatigue, delirium, syncope, somnolence, agitation, dizziness and hallucinations. Some patients experienced other behavioural changes such as aggressive reactions, personality disorders or depersonalization. Changes in pulse or blood pressure occasionally occurred.

In about two-thirds of cases, full recovery followed withdrawal of the SSRI and fluid restriction. Three cases had a fatal outcome related to hyponatraemia. Other patients had not recovered or the outcome was unknown at the time of reporting. The pattern of ADRAC reports is consistent with published findings suggesting that hyponatraemia with SSRIs is more frequent in the elderly, particularly females, and onset is mostly during

the first 30 days after commencing an SSRI (2). SIADH appears to be part of the mechanism of hyponatraemia with the SSRIs, and inhibition of serotonin reuptake may be associated with a central increase in ADH release and hence induction of SIADH (3).

A recent Australian study of elderly psychiatric patients found that use of an SSRI or venlafaxine was associated with a 3.5-fold increase in the risk of hyponatraemia after controlling for age, sex, depression status, use of other drugs associated with hyponatraemia and seriousness of physical disease (4).

Neuropsychological symptoms developing in the first month of SSRI or venlafaxine use should prompt measurement of serum electrolytes. Elderly females and patients taking diuretics are at added risk.

Extracted from Australian Adverse Drug Reaction Bulletin, Volume 22, Number 3, 2003.

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Salmeterol labelling changes

The Food and Drug Administration (FDA) has announced new safety information and warnings to be added to the labelling for drug products containing the long-acting bronchodilator, salmeterol, used to treat asthma and chronic obstructive pulmonary disease (COPD). A small but significant increased risk of life-threatening asthma episodes or asthma-related deaths have been observed.

On 23 January 2003, FDA released a talk paper announcing the preliminary results of an interim analysis of the Salmeterol Multicentre Asthma Research Trial (SMART), which compared the effects of salmeterol to placebo in patients with asthma for a period of 28 weeks. The primary endpoint was the occurrence of either respiratory-related death or a respiratory-related life-threatening experience (e.g., requirement for mechanical ventilation). Secondary endpoints included all-cause death, asthma-related death, and asthma-related death or life-threatening experience.

Although the study was intended to enrol 60 000 patients, the study was stopped by the sponsor after review of the results of a planned interim analysis after approximately half of the intended number of patients were enrolled. The analysis includes 13 174 patients treated with Serevent®, and 13 179 patients treated with placebo. The analysis showed no significant difference between treatment groups for the primary endpoint, however, a higher number of asthma-related deaths (13 vs. 4), and a higher number of asthma-related deaths or life-threatening experiences (36 vs. 23) were observed in the Serevent® group compared to placebo.

The SMART study was not designed to analyse differences in outcome based on demographic characteristics but post-hoc subgroup analyses based on race and ethnicity were conducted. These analyses showed no increase in respiratory- or asthma-related events among Caucasian patients. For African-American patients there was a statistically significant increase in primary events (respiratory-related death or life-threatening experience) in the Serevent® group (20 vs. 7). In addition, the occurrence of asthma-related death (8 vs. 1) and asthma-related death or life-threatening experience (19 vs. 4) was statistically significantly greater in African-American patients compared to placebo.

The Food and Drug Administration (FDA) emphasizes that based on available data the benefits of treatment with salmeterol in patients with asthma and COPD continue to outweigh the potential risks when used according to the instructions contained in the product labelling. Patients are advised not to stop taking products without first consulting their physicians.

Reference: *FDA Talk Paper*, T03-62, 14 August 2003

Pregnancy during depot medroxyprogesterone use

The Australian Adverse Reactions Advisory Committee (ADRAC) has received 27 reports of women becoming pregnant despite using depot medroxyprogesterone products (Depo-Provera®, Depo-Ralovera®) for contraception. In ten of the cases, the woman was confirmed as becoming pregnant 2–10 weeks after administration of the drug. An interaction with carbamazepine may have been a factor in two of these cases. In another nine cases, the injections were given late or at borderline times.

These depot progesterone contraceptives have a high level of efficacy (1). However, prescribers and other health care professionals who administer these drugs need to avoid the following situations which contribute to the risk of contraceptive failure:

- Incorrect timing of the injection — injections must be commenced during the first five days after the onset of a normal menstrual period, within five days postpartum if not breast-feeding or, if breast-feeding, at six weeks post-partum, after having excluded pregnancy. Injections are given at 3-monthly intervals, no more than 14 weeks apart. If the interval is greater than 14 weeks, a pregnancy test should be conducted prior to administration.
- Failure to properly suspend the microcrystals by not adequately shaking the vial. Storing vials on their side may allow the microcrystals to cake and fail to suspend when shaken.
- Failure to give the full dose — inadequate drawing up or full dose not injected.
- Incorrect injection technique with deposition of the suspension in tissues superficial to the muscles.
- Incorrect drug being administered — there has been one case of Depo-Medrol® being used instead of Depo-Provera®.

Extracted from Australian Adverse Drug Reaction Bulletin, Volume 22, Number 3, 2003.

Reference: Borgatta, L., Murthy, A., Chuang, C. et al. Pregnancies diagnosed during Depo-Provera® use. *Contraception*, **66**: 169–172 (2002).

Etonogestrel and vaginal bleeding

Since August 2001, the Australian Adverse Reactions Advisory Committee (ADRAC) has received 130 adverse reaction reports for Implanon® (subdermal etonogestrel contraceptive implant), including 37 reports of vaginal bleeding, most of which described prolonged bleeding (duration 2–26 weeks; median 8 weeks). The bleeding generally started soon after insertion, but the time to onset was up to 16 weeks. Thirty-three of the 37 patients required implant removal. One patient was hospitalized, and transfused 4 units of packed red blood cells.

In a published 3-year study, 2.8% of patients experienced heavy or prolonged bleeding with Implanon® (1). Unacceptable vaginal bleeding may occasionally occur and often requires implant removal.

Extracted from Australian Adverse Drug Reaction Bulletin, Volume 22, Number 3, 2003.

Reference: Croxatto, H.B. Clinical profile of Implanon®: a single-rod etonogestrel contraceptive implant. *European Journal of Contraception and Reproductive Health Care*, 5(Suppl 2): 21–28 (2000).

Hepatic reactions with minocycline

Minocycline is an effective long-term treatment for severe acne, but is associated with serious adverse reactions, including rare cases of hepatic dysfunction. In one study, the incidence of hepatic reactions in new users was one case/10 000 person-months (1).

ADRAC has received 42 reports of hepatic reactions with minocycline including 21 of hepatitis. It was the only drug taken by most of these patients, and was used for acne by 28. Fifteen patients were under 21 years of age. Where liver enzyme results were provided, they showed a hepatocellular pattern (12) more often than a cholestatic (3) or mixed picture (2). Time to onset was provided in 13 reports and suggested that cholestatic reactions occurred earlier (= 4 weeks) than hepatocellular damage (usually after months or years). Of the 42 cases, 25 had recovered by the time of reporting, usually in less than 12 weeks. None of the patients died or required liver transplantation.

A published case series suggests that hepatic reactions with minocycline may present either with features of a hypersensitivity syndrome (onset within 35 days) or resemble autoimmune chronic active hepatitis (onset after months or years) (2). Despite well-documented reports, no ADRAC cases conformed to the criteria for a hypersensitivity syndrome. However, five reports were suggestive of an autoimmune reaction. All cases had antinuclear antibodies, and one had other features of lupus erythematosus. A time to onset of 11 or 12 months was specified in two cases.

Other serious adverse reactions associated with minocycline include CNS effects, skin discolouration and benign intracranial hypertension. Prescribers are particularly advised to note that hepatitis developing in a patient on long-term minocycline may be indistinguishable from autoimmune hepatitis both serologically and histologically. Discontinuation of minocycline usually results in complete recovery.

Extracted from Australian Adverse Drug Reaction Bulletin, Volume 22, Number 3, 2003.

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Hepatobiliary reactions with the newer antidepressants

Health Canada continues to monitor suspected hepatobiliary adverse reactions (ARs) associated with the newer antidepressants that exert an effect on serotonin neurotransmission. These include citalopram (Celexa®), fluoxetine (Prozac®), fluvoxamine (Luvox®), mirtazapine (Remeron®), nefazodone (Serzone-5HT₂®), paroxetine (Paxil®), sertraline (Zoloft®), trazodone (Desyre®) and venlafaxine (Effexor®). Reports of suspected hepatobiliary ARs associated with these antidepressants were submitted to Health Canada from the time of marketing to July 2002.

From the data available, no fatal outcomes were reported for hepatobiliary ARs associated with these antidepressants. In two reports involving nefazodone, liver transplantation was required. In three other reports involving nefazodone liver transplantation was considered, but the patients' conditions eventually improved after prolonged hospital care. The time of onset of liver injury ranged from 1 to 4 months. None of these five patients had a prior history of liver disease.

The current literature documents several cases of severe hepatic failure associated with nefazodone. The US Food and Drug Administration (FDA) recently included a black-box warning in Serzone® package insert, stating that the reported rate in the United States of liver failure resulting in death or liver transplantation is about 1 case per 250 000–300 000 patient-years of treatment. This rate is about 3–4 times the estimated background rate of liver failure. It is possibly an underestimate of true risk because of underreporting.

At present, there is no way to predict in which patient liver failure is likely to develop. Ordinarily, treatment with nefazodone should not be initiated in patients with active liver disease or with an elevated baseline serum transaminase level. Although it is unclear whether periodic liver function tests can help prevent serious liver injury, it is generally believed that early detection of drug-induced hepatic injury along with immediate discontinuation of the suspected drug enhances the likelihood of recovery.

*Mano Murty, Iza Morawiecka, Suniti Sharma.
Canadian Adverse Reaction Newsletter,
13(1), January 2003*

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Convulsions with newer-generation antihistamines

Antagonists of histamine H₁ receptors are commonly classified as first-generation or new-generation antihistamines based on their frequent sedating effect at therapeutic doses. The “newer-generation” antihistamines, also known as second- or third-generation antihistamines, include astemizole, cetirizine, desloratadine, fexofenadine, loratadine and terfenadine, and were developed as nonsedating alternatives to the first-generation compounds. The sale of terfenadine and astemizole was stopped in Canada because of associated QT prolongation, which could lead to torsades de pointes or ventricular fibrillation. Loratadine, cetirizine, fexofenadine and desloratadine have been marketed in Canada since 1988, 1991, 1997 and 2002, respectively. Loratadine, fexofenadine and desloratadine are available as nonprescription drugs. Cetirizine is available as both a nonprescription and prescription drug.

Seizures or convulsions have been reported in the literature with some first-generation antihistamines (chlorpheniramine, diphenhydramine, pheniramine and pyribenzamine) as well as with some newer-generation antihistamines (astemizole, cetirizine, fexofenadine, loratadine and terfenadine). According to the US Food and Drug Administration Adverse Event Reporting System (July 1999), convulsions associated with ceti-

rizine, fexofenadine and loratadine accounted for 2.5%, 3.1% and 2.1% respectively of the total adverse events reported with these drugs.

From their respective dates of marketing in Canada to 19 September 2002, Health Canada received 20 reports of suspected convulsive disorders associated with the use of loratadine (9), cetirizine (7) and fexofenadine (4). There have been no reports of suspected convulsive disorders associated with desloratadine at this time. Reports of seizures and convulsions accounted for 3.6%, 1.4% and 0.9% of the total number of adverse reactions (ARs) reported with loratadine, cetirizine and fexofenadine respectively. Fifteen of the 20 cases occurred in patients with a prior history of seizures or in those who used anticonvulsant drugs concomitantly. However, these data must be interpreted with caution, as causality has not been confirmed. It is unclear whether newer-generation antihistamines aggravate the medical condition of patients with a history of seizures or whether they interact with anticonvulsants. Further studies and continued monitoring of these agents regarding their role in causing seizures or convulsions, especially in patients predisposed to convulsive disorders, are required.

Also of note are two reports of patients who apparently took more than the recommended daily dose of the drug. One report involved a 27-year-old woman receiving phenytoin therapy who had been seizure free for over 2 years. She took 3 doses of cetirizine (20 mg each) in 24 hours and experienced a seizure 1+ hours after the third dose. The maximum recommended daily dose of cetirizine is 20 mg. The other report was of a healthy 37-year-old man with no history of seizures who experienced 2 grand mal seizures, 3 hours apart, after 3 days of taking 25 mg of loratadine daily (in the form of 2 tablets of Claritin® and 1 tablet of Claritin Extra®). The patient had also ingested alcohol (+ beer) the night before the seizure. The recommended daily adult dose of loratadine is 10 mg.

Patients should be reminded to read package labels carefully and not to exceed the recommended or maximum daily dose of any therapeutic health product, including nonprescription drugs. Patients should also be made aware that multiple products may contain the same active ingredients and to consult their health care professional for further information.

Pascale Springuel, Duc Vu, Canadian Adverse Reaction Newsletter, 13(1), January 2003

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Rifampicin and pyrazinamide not to be used for latent tuberculosis infection

The Centers for Disease Control (CDC) has reported severe liver injury in patients treated for latent tuberculosis infection (LTBI) with a daily and twice-weekly 2-month regimen of rifampicin (US: rifampin) with pyrazinamide (RZ). On the basis of these initial reports, CDC has cautioned clinicians in the use of this therapy. To estimate the incidence of RZ-associated severe liver injury CDC collected data from cohorts of patients in the United States who received RZ for the treatment of LTBI. Analysis found high rates of hospitalization and death from liver injury associated with the use of RZ. On the basis of these findings, the American Thoracic Society (ATS) and CDC now recommend that this regimen should generally not be offered to persons with LTBI.

The revised ATS/CDC recommendations are endorsed by the Infectious Diseases Society of America (IDSA). Clinicians are advised to use the recommended alternative regimens for the treatment of LTBI. Rifampicin and pyrazinamide

(PZA) should continue to be administered in multidrug regimens for the treatment of persons with active tuberculosis (TB) disease.

This regimen should generally not be offered to persons with LTBI for either HIV-negative or HIV-infected persons and should never be offered to patients who:

- are concurrently taking other medications associated with liver injury;
- drink excessive amounts of alcohol, even if alcohol use is discontinued during treatment;
- have underlying liver disease; or
- have a history of isoniazid (INH)-associated liver injury.

If the potential benefits of this regimen outweigh the risk for severe liver injury and death associated with it, use of RZ might be considered in carefully selected patients, but only if:

- the preferred or alternative regimens (i.e., 9 months of daily or biweekly INH, 6 months of daily or biweekly INH, or 4 months of daily rifampicin) are judged not likely to be completed and
- oversight by a clinician with expertise in the treatment of LTBI can be provided.

A TB/LTBI expert should be consulted before RZ is offered. In addition, patients should be asked whether they have had liver disease or adverse effects from taking INH or other drugs, informed of potential hepatotoxicity of the RZ regimen, and advised against the concurrent use of potentially hepatotoxic drugs, including over-the-counter drugs such as paracetamol (acetaminophen).

To facilitate periodic clinical assessments of persons taking an RZ regimen (clinicians should dispense no more than a 2-week supply (with a daily PZA dose of <20.0 mg/kg/d [maximum daily PZA dose: 2.0 g], and a twice-weekly dose of <50.0 mg/kg/d [maximum twice-weekly PZA dose: 4.0 g]).

Patients should be reassessed in person by a health-care provider at 2, 4, 6, and 8 weeks of treatment for adherence, tolerance, and adverse effects. The 8-week assessment also should be used to document treatment completion. At each visit, health-care providers who speak the patient's own language should instruct the patient to stop taking RZ immediately and seek medical consultation if abdominal pain, emesis, jaundice, or other symptoms of hepatitis develop. Provider continuity is recommended for optimal monitoring.

For persons taking this regimen, serum aminotransaminases (AT) and bilirubin should be measured at baseline and at 2, 4, 6, and 8 weeks of treatment. Because the majority of these patients had onset of symptoms of liver injury after the fourth week of therapy they should be monitored throughout the entire course of treatment. Use of RZ should be discontinued immediately and not resumed for any of the following findings:

- AT greater than five times the upper limit of normal range in an asymptomatic person,
- AT greater than normal range when accompanied by symptoms of hepatitis, or
- a serum bilirubin concentration greater than the normal range, whether or not symptoms are present.

The risk for progression from LTBI to active TB is increased substantially in persons with HIV infection. Therefore, as recommended previously for the treatment of all persons in whom LTBI is diagnosed, voluntary HIV counselling and testing should be offered routinely.

Recommendations against the use of RZ for treatment of LTBI do not apply to the appropriate use of rifampicin and PZA in multidrug regimens for the treatment of persons with active TB disease.

Reference: CDC. Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampicin and Pyrazinamide for Treatment of Latent Tuberculosis Infection. *Morbidity and Mortality Weekly Report*, 52: 735–739 (2003).

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

Individual Drugs

The role of statins in primary prevention

Two important questions regarding statin therapy are:

- What is the overall health impact when statins are prescribed for primary prevention?
- Should the dose of statin be titrated to achieve target lipid levels?

Three new randomized controlled trials (1–3) help answer the first question.

Estimating the overall health impact of statins in primary prevention requires balancing possible benefits and possible harms. The benefit is estimated by combining two cardiovascular serious adverse events known to be reduced by statins in secondary prevention trials: total myocardial infarction (fatal and non-fatal) (5) and total stroke (fatal and non-fatal) (6). The balance between benefit and harm (overall health impact) is estimated by total mortality and total serious adverse events. Serious adverse events include any untoward medical occurrence that results in death, is life threatening, requires hospitalization or prolongation of hospitalization, or results in persistent or significant disability.

PROSPER

Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (1) studied the effect of pravastatin compared to placebo in two older populations of patients: 56% primary prevention (no past or symptomatic cardiovascular disease) and 44% secondary prevention (past or symptomatic cardiovascular disease) (Table 1). Pravastatin did not reduce total myocardial infarction or total stroke in the primary prevention population, RR 0.94 [0.78 – 1.14], but did so in the secondary prevention population, RR 0.80 [0.68 – 0.94], ARR 4.3%, NNT 23 for 3.2 years. Measures of overall health impact in the combined populations, total mortality and total serious adverse events, were unchanged by pravastatin as compared to placebo, RR 0.98 [0.84 – 1.14] and 1.01 [0.96 – 1.06], respectively.

ALLHAT-LLT

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) (2) was designed to determine whether pravastatin compared with usual care reduces all-cause mortality in older, moderately hypercholesterolaemic, hypertensive patients with at least one additional coronary heart disease risk factor. The published data is for the whole population, 86% of which was primary prevention. Pravastatin did not reduce total myocardial infarction and total stroke, RR 0.91 [0.82 – 1.01]. Pravastatin also did not reduce total mortality, RR 0.99 [0.89 – 1.09]. Total serious adverse events were not reported.

Table 1 (abridged): Characteristics of the 5 major statin primary prevention trials

Trial	Drug Name	Dose mg/day	N	Average age (yrs)	% Primary Prevention
PROSPER	pravastatin	40	5804	75	56
ALLHAT-LLT	pravastatin	40	10 355	66	86
ASCOT-LLA	atorvastatin	10	10 305	63	82
AFCAPS	lovastatin	20-40	6605	58	100
WOSCOP	pravastatin	40	6595	55	92

* % reduction in the statin group minus the control group after 1 to 2 years of therapy.
N = total number of patients in trial

ASCOT-LLA

The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) was designed to assess the benefits of atorvastatin versus placebo in hypertensive patients with average or lower-than-average cholesterol concentrations and at least three other cardiovascular risk factors. The published data is for the whole population, 82% of which was primary prevention. The trial was originally planned for 5 years, but was stopped after a median follow-up of 3.3 years because of a significant reduction in cardiac events. Atorvastatin reduced total myocardial infarction and total stroke, RR 0.82 [0.70 – 0.96], ARR 1.2%, NNT 83. Total mortality was not significantly reduced, RR 0.87 [0.71 – 1.05]. The trial report stated that total serious adverse events did not differ between patients assigned atorvastatin or placebo, but the actual numbers of serious adverse events were not given.

Overall health impact when statins are prescribed for primary prevention

To answer this question we combined the data from the 5 mostly primary prevention trials, the 3 above plus 2 published earlier (Tables 1 and 2). These calculations reflect a population that is 84% primary prevention and 16% secondary prevention. In the pooled data the statins reduced the cardiovascular measures, total myocardial infarction and total stroke by 1.4% as compared to control. This value indicates that 71 mostly primary prevention patients would have to be treated for 3 to 5 years to prevent one such event. This can be compared with the same pooled outcome in 4 large secondary prevention statin trials, ARR 4.8%, NNT 21 for 5 years (4).

In the 2 trials where serious adverse events are reported, the 1.8% absolute reduction in myocardial infarction and stroke should be reflected by a similar absolute reduction in total serious adverse events; myocardial infarction and stroke are, by definition, serious adverse events. However, this is not the case; serious adverse events are similar in the statin group, 44.2%, and the control group, 43.9% (Table 2). This is consistent with the possibility that unrecognized serious adverse events are increased by statin therapy and that the magnitude of the increase is similar to the magnitude of the reduction in cardiovascular serious adverse events in these populations. This hypothesis needs to be tested by analysis of total serious adverse event data in both past and future statin trials. Serious adverse event data is available to trial authors, drug companies and drug regulators. The other measure of overall impact, total mortality, is available in all 5 trials and is not reduced by statin therapy

Conclusions

- If cardiovascular serious adverse events are viewed in isolation, 71 primary prevention patients with cardiovascular risk factors have to be treated with a statin for 3 to 5 years to prevent one myocardial infarction or stroke.
- This cardiovascular benefit is not reflected in 2 measures of overall health impact, total mortality and total serious adverse events. Therefore, statins have not been shown to provide an overall health benefit in primary prevention trials.

Extracted from Therapeutics Letter, Number 48, <http://www.ti.bc.ca>

Outcome	Statin		Control		RR [95% CI]		ARR		NNT (3-5 yr)	
	5 trials	2 trials*	5 trials	2 trials*	5 trials	2 trials*	5 trials	2 trials*	5 trials	2 trials*
Total mortality	6.6	6.1	6.9	6.2	0.95 [0.88-1.02]	0.99 [0.87-1.14]				
Total MI and stroke	7.3	8.0	8.7	9.8	0.84 [0.78-0.90]	0.82 [0.78-0.90]	1.4	1.8	71	56
Total SAEs*		44.2		43.9		1.01 [0.97-1.05]				

* AFCAPS and PROSPER MI = Myocardial Infarction SAEs = Serious Adverse Events RR = Relative Risk. CI = Confidence Interval ARR = Absolute Risk Reduction NNT = Number Needed to Treat to prevent one event.

Comments from Management of Noncommunicable Diseases (NMC), World Health Organization

The ASCOT-LLA was ended early after an interim analysis showed an outcome in favour of statin treatment. However, the additional benefit to effective lowering of blood pressure by statin therapy is not impressive in absolute terms. The study population was mostly men/white, mean age 63, average of 3.7 risk factors in addition to hypertension. In other words, patients at rather high cardiovascular risk. Further statin treatment lowered total cholesterol by 1.3 mmol and blood pressure was well controlled; both factors contributing to the outcome.

On the other hand, the ALLHAT LLT trial patients had hypertension with at least one cardiovascular risk factor. The difference in total cholesterol between groups during the trial was only around 0.5 mmol/L and the trial failed to show any benefit in all-cause mortality (primary outcome) or in non fatal myocardial infarction and non-fatal coronary heart disease (secondary outcome).

The above findings, and the results of the other studies reiterate:

1. That the safety of statins have to be proven in people with low coronary heart disease risk. However, extremely large trials are required to demonstrate the safety of statins in terms of overall mortality in such subjects.
2. That treatment strategies in primary prevention of cardiovascular disease should depend on global cardiovascular risk assessment rather than on numerical values of individual risk factors.

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A strategy to reduce cardiovascular disease by more than 80% ?

Heart attacks, stroke, and other preventable cardiovascular diseases kill or seriously affect many populations. Western diet and lifestyle increase levels of risk factors and their combined effects have made these diseases common. Cardiovascular disease can be avoided or delayed, but the necessary changes to Western diet and lifestyle are not practicable in the short term. Randomized trials show that drugs to lower three risk factors—low density lipoprotein (LDL) cholesterol, blood pressure, and platelet function (with aspirin)—reduce the incidence of ischaemic heart disease (IHD) events and stroke. Evidence that lowering serum homocysteine (with folic acid) reduces the risk of these diseases is largely observational but still compelling.

With this in mind, a meta-analysis has recently been carried out in the United Kingdom (1) to determine the combination of drugs and vitamins to achieve prevention of cardiovascular disease with minimal adverse effects as a single daily poly pill (2). The strategy would simultaneously reduce four cardiovascular risk factors: low-

density lipoprotein cholesterol, blood pressure, serum homocysteine, and platelet function, regardless of pretreatment levels.

The following polypill formulations are proposed:

- a statin: e.g. atorvastatin or simvastatin;
- three blood pressure lowering drugs: e.g. a thiazide, beta blocker, and angiotensin converting enzyme (ACE) inhibitor;
- folic acid; and
- aspirin.

The polypill is estimated to reduce IHD events by 88% and stroke by 80%. One-third of people taking this pill from age 55 would therefore benefit — gaining on average about 11 years of life free from an IHD event or stroke. Summing the adverse effects of the components observed in randomized trials showed that the polypill would cause symptoms in 8–15% of people depending on the precise formulation. The authors propose that this strategy could largely prevent heart attacks and stroke if taken by everyone aged 55 and older and everyone with existing cardiovascular disease. It would be acceptably safe and with widespread use would have a greater impact on the prevention of disease in the Western world than any other single intervention.

A large preventive effect would require intervention in everyone at increased risk irrespective of the risk factor levels; intervention on several reversible causal risk factors together; and reducing these risk factors by as much as possible.

A low-cost polypill could use generic components that are no longer subject to patent protection. This formulation does not have the lowest rate of adverse effects, but even if about 10% of people were intolerant of the formulation it would still have considerable public health merit. Those found to be intolerant could be prescribed alternatives to avoid the side effects. Controlled trials of different formulations of the polypill would provide direct estimates of acceptability.

The preventive strategy outlined is radical. But the authors argue that a formulation that prevented all cancer and was safe would undoubtedly be widely used, and one that prevented more than 80% of cardiovascular disease would be even more important because such deaths are more common than cancer deaths. It is also pointed out that in Western society the risk factors are high and everyone is at risk. The diseases they cause are common and often fatal and there is much to gain and little to lose by the widespread use of these drugs. No other preventive method would have so great an impact on public health in the Western world.

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Aspects of Quality Assurance

Pre-qualification of HIV drugs

The Pilot Procurement, Quality and Sourcing Project for HIV Drugs was created in October 2000 by WHO, UNICEF, UNFPA, and UNAIDS, with support from the World Bank. Its objective is to pre-qualify manufacturers of medicines for HIV (antiretrovirals) and HIV-related illnesses (anti-infectives, anticancer medicines, and pain killers) as suppliers to United Nations and other public sector drug procurement agencies. Medicines for the treatment of HIV infection have been selected because they remain largely inaccessible in those countries that are most affected by HIV/AIDS.

For antiretrovirals, there is currently limited regulatory experience, and well-established quality standards such as pharmacopoeial monographs are not generally available. The overall aim of the project is to provide pre-qualification and quality assessment of a selected number of pharmaceutical products considered for purchase by UN agencies involved in the procurement of medicines and diagnostics. WHO manages the project and provides technical support and assistance. UNICEF provides administrative support and infrastructure. A spin-off objective is to develop a harmonized quality assessment system for use by public sector procurement agencies.

Progress in pre-qualification has been reported in Volume 16, Number 1 of this journal. The present summary considers experience in pre-qualification of generic HIV medicines and includes the eighth cumulative list of combined innovator and generic products published on 20 August 2003.

Access to generic antiretrovirals

In 2002, the number of people living with HIV/AIDS reached 42 million, with 5 million newly infected cases annually (1). Addressing this crisis demands not only rapid expansion of HIV/AIDS prevention, but also scaling up of treatment and care, including access to HIV/AIDS medicines such as antiretrovirals (ARVs) (2).

Antiretroviral triple-therapy has been effective in industrialized countries in the fight against HIV. However, affordable ARVs are not available in sufficient quantity where they are most needed — Africa, Central and Eastern Europe, and throughout much of Asia and Latin America. Oxfam has recently reported that generic competition can lead to a dramatic drop in prices of AIDS medicines. In Uganda, prices fell by as much as 78% in a few months and by as much as 97% in a 2-year period. The number of patients taking ARVs at one treatment centre increased by 200% within a year (3).

The supply of medicines used in the treatment of HIV/AIDS has become a major concern at both

international and country level (5). In addition, recent efforts to accelerate access to HIV-related medicines through negotiation and generic competition have highlighted the importance of ensuring that only quality medicines are procured. Several factors prevent the wider distribution of quality generic ARVs. One of these is the lack of well-established quality specifications and limited experience among generic medicine manufacturers. Efficient procedures therefore need to be in place for compliance and successful pre-qualification of potential suppliers of quality products (2, 5–10).

Pilot procurement, quality and sourcing project for HIV drugs

WHO and UNICEF recognize that the generic pharmaceutical industry has a vital role to play in efforts to provide safe and effective medicines at low cost (4). The purpose of the Pilot Procurement, Quality and Sourcing Project for HIV Drugs (6) is to assess quality, safety and efficacy of products and manufacturing sites. Following assessment of product dossiers and visits to manufacturing facilities by WHO inspectors, pre-

qualified suppliers are confirmed as a reliable supplier and published in a list available on the project website (<http://www.who.int/medicines>) (6).

Pre-qualification process

Demands for expressions of interest from manufacturers and/or suppliers wishing to take part in the pre-qualification procedure have been regularly published by WHO and other UN agencies. The project objectives have focused on prequalification of the following ARVs (2).

non-nucleoside reverse transcriptase inhibitors:

delavirdine, efavirenz, nevirapine

nucleoside reverse transcriptase inhibitors:

abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine, lamivudine + zidovudine

protease inhibitors:

amprenavir, indinavir, nelfinavir, ritonavir, saquinavir, lopinavir + ritonavir

Specific instructions are provided to manufacturers on how to compile product dossiers and provide relevant data and information on quality, safety and efficacy to comply with WHO standards (6–10). These instructions are available on the project website (6).

Between June 2001 and March 2003, WHO-appointed evaluators have assessed 65 generic ARV product dossiers. The pre-qualification of products, suppliers and manufacturers has been a positive exercise. Of the 65 generic ARV product dossiers submitted for assessment, 14 (21%) were immediately confirmed as meeting WHO recommended international standards (see list on page 160).

For those products and manufacturers not meeting WHO standards, information and advice is provided on how this can be achieved. In many cases, non-compliance occurred because different requirements for registration and licensing of multisource (generic) products (7) are operational within and between countries. For example, bio-equivalence studies may often not be required by some national drug regulatory authorities. Several generic manufacturers have none the less been willing to undertake additional studies (9) including stability testing under WHO

recommended conditions as well as bioequivalence studies to ensure compliance of their products with international standards, while manufacturers not meeting WHO good manufacturing practices (GMP) (10) have undertaken to upgrade facilities and implement corrective action.

The latest list of pre-qualified products and manufacturers is set out on pages 158–160 and is also available on the project website (6).

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List of pre-qualified products: 20 August 2003

INN	strength	dosage form	supplier	site	packaging
abacavir	300 mg	tablet	GlaxoSmithKline	UK	blister
abacavir	20 mg/ml	oral solution	GlaxoSmithKline	UK	HDPE (bottle)
abacavir	800 mg	dispersable tablet	Cipla	India	blister
abacavir	5%	cream	Cipla	India	Al tube
abacavir	200 mg	tablet	Ranbaxy	India	blister
abacavir	400 mg	tablet	Ranbaxy	India	blister
aciclovir	800 mg	tablet	Ranbaxy	India	blister
amprenavir	15 mg/ml	oral solution	GlaxoSmithKline	UK	HDPE (bottle)
amprenavir	50 mg	capsule	GlaxoSmithKline	France	HDPE (bottle)
	150 mg				
ceftriazone	500 mg	inj. subst.	Roche	Switzerland	glass vials
ceftriazone	250 mg	inj. subst.	Roche	Switzerland	glass vials
ciprofloxacin	750 mg	tablet	Lab. Cinfa	Spain	blister
ciprofloxacin	500 mg	tablet	Lab.Cinfa	Spain	blister
ciprofloxacin	250 mg	tablet	Lab.Cinfa	Spain	blister
ciprofloxacin	100 mg	tablet	Cipla	India	blister
ciprofloxacin	250 mg	tablet	Cipla	India	blister
ciprofloxacin	500 mg	tablet	Cipla	India	blister
ciprofloxacin	750 mg	tablet	Cipla	India	blister
ciprofloxacin	250 mg	tablet	Ranbaxy	India	blister (PVC/Al)
ciprofloxacin	500 mg	tablet	Ranbaxy	India	blister (PVC/Al)
ciprofloxacin	750 mg	tablet	Ranbaxy	India	blister (PVC/Al)
clarithromycin	250 mg	tablet	Ranbaxy	India	blister (PVC/PVDC/Al)
clarithromycin	500 mg	tablet	Ranbaxy	India	blister (PVC/PVDC/Al)
cotrimoxazole	200 + 40 mg	syrup	Roche	Switzerland	amber glass bottle
cotrimoxazole	800 +160 mg	tablet	Roche	Switzerland	blister (PVC/Al)
cotrimoxazole	400 + 80 mg	tablet	Roche	Switzerland	blister
didanosine	25 mg	tablet	Bristol Myers Squibb	France	HDPE (bottle)
didanosine	50 mg	tablet	Bristol Myers Squibb	France	HDPE (bottle)
didanosine	100 mg	tablet	Bristol Myers Squibb	France	HDPE (bottle)
didanosine	150 mg	tablet	Bristol Myers Squibb	France	HDPE (bottle)
didanosine	200 mg	chew. or dispersable tablet	Bristol Myers Squibb	France	HDPE (bottle)
fluconazole	50 mg	capsule	Ranbaxy	India	blister
fluconazole	100 mg	capsule	Ranbaxy	India	blister
fluconazole	150 mg	capsule	Ranbaxy	India	blister
fluconazole	200 mg	capsule	Ranbaxy	India	blister
ganciclovir	500 mg	Inj. Subst.	Roche	Switzerland	glass vials
indinavir	400 mg	capsule	Hetero Drugs	India	strip (Al), HDPE bottle
lamivudine	150 mg	tablet	Hetero Drugs	India	strip (Al), HDPE bottle
lamivudine	150 mg	tablet	Ranbaxy	India	blister
lamivudine	150 mg	tablet	Cipla	India	blister
lamivudine	50 mg/5ml	solution	Cipla	India	PET (bottle)
lamivudine	150 mg	tablet	GlaxoSmithKline	UK	HDPE (bottle)
lamivudine	10 mg/ml	oral solution	GlaxoSmithKline	UK	HDPE (bottle)
lamivudine+zidovudine	150/300 mg	tablet	Ranbaxy	India	blister

INN	strength	dosage form	supplier	site	packaging
lamivudine+ zidovudine	150/300 mg	tablet	Cipla	India	blister
lamivudine+ zidovudine	150 mg + 300 mg	tablet	GlaxoSmithKline	UK	blister HDPE (bottle)
lamivudine+ zidovudine+ abacavir	150 mg+ 300 mg+ 300 mg	tablet	GlaxoSmithKline	UK	blister HDPE (bottle)
nelfinavir mesylate	250 mg	film coated tablet	Roche	Spain, Switzerland	plastic container
nelfinavir mesylate	0.50 mg /ml	oral suspension	Roche	Switzerland	HDPE (bottle)
nevirapine	200 mg	tablet	Ranbaxy	India	blister
nevirapine	200 mg	tablet	Cipla	India	blister
nevirapine	200 mg	tablet	Boehringer Ingelheim	Germany	blister
nevirapine	50 mg /5ml	oral suspension	Boehringer Ingelheim	USA	HDPE (bottle) + syringe
nevirapine	200 mg	tablet	Hetero Drugs	India	strip (Al) HDPE (bottle)
ritonavir	100 mg	capsule	Abbott Laboratories	USA France	HDPE (bottle)
ritonavir	80 mg/ml	oral solution	Abbott Laboratories	UK	PET (bottle)
ritonavir+ lopinavir	33,3 mg + 133,3	capsule	Abbott Laboratories	USA	HDPE (bottle)
ritonavir+ lopinavir	20 mg + 80 mg/ml	oral solution	Abbott Laboratories	UK	PET (bottle)
saquinavir	200 mg	soft capsule	Roche	Germany	glass bottle
saquinavir	200 mg	capsule	Roche	Switzerland	glass bottle
stavudine	15 mg	capsule	Bristol Myers Squibb	France	blister HDPE (bottle)
stavudine	20 mg	capsule	Bristol Myers Squibb	France	blister HDPE (bottle)
stavudine	30 mg	capsule	Bristol Myers Squibb	France	blister HDPE (bottle)
stavudine	40 mg	capsule	Bristol Myers Squibb	France	blister HDPE (bottle)
sulfadiazine	500 mg	tablet	Doms Recordati	France	blister
vinblastine sulfate	10 mg /10 ml	injection	Cipla	India	vial
vincristine sulfate	1mg/ml	injection	Cipla	India	vial
zalcitabine	0.375 mg	tablet	Roche	USA Switzerland	blister (Al) glass bottle
zalcitabine	0.75 mg	tablet	Roche	USA	blister (Al) glass bottle
zidovudine	100 mg	capsule	Combino	Spain	strip (Al)
zidovudine	250 mg	capsule	Combino	Spain	blister PVC/Al
zidovudine	300 mg	capsule	Combino	Spain	blister PVC/Al
zidovudine	300 mg	tablet	Ranbaxy	India	blister
zidovudine	300 mg	tablet	Cipla	India	blister
zidovudine	100 mg	capsule	Cipla	India	HDPE (bottle)
zidovudine	50 mg/5ml	solution	Cipla	India	PET (bottle)

INN	strength	dosage form	supplier	site	packaging
zidovudine	100 mg	capsule	GlaxoSmithKline	UK	blister amber glass bottle
zidovudine	250 mg	capsule	GlaxoSmithKline	UK	blister
zidovudine	10 mg/ml	infusion	GlaxoSmithKline	USA	amber glass vial
zidovudine	50 mg/5 ml	oral solution	GlaxoSmithKline	UK	amber glass bottle
zidovudine	300 mg	tablet	GlaxoSmithKline	UK	blister (PVC/Al) amber glass bottle
zidovudine	300 mg	tablet	Hetero Drugs	India	strip (Al) HDPE bottle

Al: aluminium

HDPE: high density polyethylene

PET: polyethylene terephthalate

PVC: polyvinyl chloride

PVDC: polyvinylidene chloride

*More information on pre-qualification/assessment of manufacturing sites is available on the project website at <http://www.who.int/medicines>

List of generic antiretroviral products and manufacturers				
INN	strength	dosage form	supplier	country of origin
indinavir	400 mg	capsule	Hetero Drugs	India
lamivudine	150 mg	tablet	Hetero Drugs	India
lamivudine	150 mg	tablet	Ranbaxy	India
lamivudine	150 mg	tablet	Cipla	India
lamivudine	50 mg/5 ml	solution	Cipla	India
lamivudine + zidovudine	150/300 mg	tablet	Ranbaxy	India
lamivudine + zidovudine	150/300 mg	tablet	Cipla	India
nevirapine	200 mg	tablet	Ranbaxy	India
nevirapine	200 mg	tablet	Cipla	India
nevirapine	200 mg	tablet	Hetero Drugs	India
zidovudine	100 mg	capsule	Combino	Spain
zidovudine	250 mg	capsule	Combino	Spain
zidovudine	300 mg	capsule	Combino	Spain
zidovudine	300 mg	tablet	Ranbaxy	India
zidovudine	300 mg	tablet	Cipla	India
zidovudine	100 mg	capsule	Cipla	India
zidovudine	50 mg/5 ml	solution	Cipla	India
zidovudine	300 mg	tablet	Hetero Drugs	India

Consultation Document

The International Pharmacopoeia – monographs for antiretrovirals

Within the framework of the Pilot Procurement Project for Quality and Sourcing of HIV Drugs, the International Pharmacopoeia is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governmental and regulatory bodies, to provide specifications and monographs for the following antiretroviral agents:

abacavir, didanosine, efavirenz, indinavir, lamivudine, nelfinavir,
nevirapine, ritonavir, saquinavir, stavudine, zidovudine

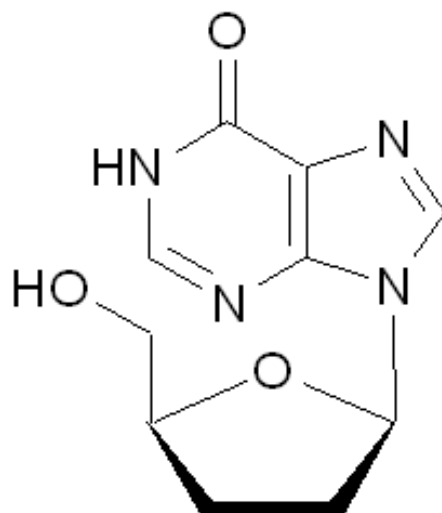
It is planned to develop specifications for the respective dosage forms in a second phase of the project. The first draft monograph, didanosine, is now available for consultation as presented below. Comments are welcome and should be sent to: Quality and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland or: kopps@who.int

DIDANOSINUM ***Didanosine***

Molecular formula: C₁₀H₁₂N₄O₃

Relative Molecular Mass: 236.23

Graphic formula:



Chemical name: 9-[(2*R*,5*S*)-5-(hydroxymethyl)tetrahydrofuran-2-yl]-1,9-dihydro-6*H*-purin-6-one; 9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-1,9-dihydro-6*H*-purin-6-one; 2',3'-dideoxyinosine (DDI); CAS Reg. No. 69655-05-6.

Description: White to almost-white powder.

Solubility: Sparingly soluble in water; slightly soluble in methanol R and ethanol (~750 g/l) TS.

Category: Antiretroviral (nucleoside reverse transcriptase inhibitor).

Storage: Didanosine should be kept in a well-closed container.

REQUIREMENTS

General requirement: Didanosine contains not less than 98.5% and not more than 101.0% of $C_{10}H_{12}N_4O_3$, calculated with reference to the dried substance.

Identity test

Carry out the examination as described under "Spectrophotometry in the infrared region" (*International Pharmacopoeia*, Vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from didanosine RS.

If the spectra obtained are not concordant, dissolve the sample in a small amount of methanol R, evaporate and carry out the IR spectrum as mentioned above. Treat didanosine RS in the same way.

Specific Optical Rotation. Use a 10 mg/ml solution and calculate with reference to the dried substance, determined in a 1.0% w/v solution in water; $[\alpha]_D^{20} = -24.0^\circ$ to -28.0° .

Heavy metals. Use 1.0 g for the preparation of the test solution as described under "Limit test for heavy metals", Procedure 1 (Vol. 1, p. 118); determine the heavy metal content according to Method A (Vol. 1, p. 119); not more than 20 µg/g.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry for 4 hours at 105 °C; it loses not more than 5 mg/g.

Related Substances. *Note: Prepare fresh solutions and perform the tests without delay*

Carry out the test as described under "High-performance liquid chromatography" (Vol. 5, p. 257), using a stainless steel column (25 cm x 4.6 mm), packed with octadecylsilyl base-deactivated silica gel for chromatography R (5µm). (Hypersil BDS is suitable)

The mobile phases for gradient elution consist of a mixture of aqueous phase (mobile phase A) and methanol (mobile phase B), using the following conditions:

Mobile phase A: A 0.05 M solution of ammonium acetate R adjusted to pH 8.0 using a 20% v/v ammonia solution.

Mobile phase B: methanol.

Time (min)	Mobile phase A (%)		Mobile phase B (%)	
	0		90	10
18	90		10	
30	75		25	
35	75		25	
40	90		10	
45	90		10	

Prepare the following three solutions in a mixture of 90 volumes of mobile phase A and 10 volumes of mobile phase B (dissolution solvent):

For solution (1), dissolve 5 mg of hypoxanthine R and 5 mg of inosine R in the dissolution solvent and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml in 10.0 ml with the same solvent.

For solution (2), dissolve 25 mg of didanosine in the dissolution solvent and dilute to 50.0 ml with the same solvent.

For solution (3), dilute 5.0 ml of solution (2) to 50.0 ml with the dissolution solvent. Then dilute 5.0 ml of this solution to 50.0 ml with the same solvent.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 254 nm.

Inject 20 μ l of solution (1). The test is not valid unless the resolution factor between the peaks due to hypoxanthine and inosine is greater than 8.0, if necessary reduce the amount of methanol in the mobile phase and adjust the proportion of aqueous phase pH 8.0 accordingly.

Inject separately 20 μ l of solution (3) in replicate injections in the chromatographic system. The relative standard deviation for peak areas of didanosine in replicate injections of solution (3) is not more than 2.0%.

Inject separately 20 μ l each of solution (2) and of mobile phase in the chromatographic system. Examine the mobile phase chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (2).

In the chromatogram obtained with solution (2), the peaks are eluted at the following relative retention with reference to didanosine: hypoxanthine = about 0.12; inosine = about 0.26; 2'-deoxyinosine = about 0.33; 2',3'-didehydrodidanosine = about 0.73; didanosine acetate [(2S,5R)-5-(6-hydroxy-9H-purin-9-yl)-tetrahydro-2-furanyl]methyl acetate) = about 2.86.

Measure the areas of the peak responses obtained in the chromatograms from solutions (2) and (3), and calculate the content of related substances as a percentage. For the calculation of limit contents, multiply the peak areas of the following impurities by the corresponding correction factor: hypoxanthine = 0.65 and 2'-deoxyinosine = 1.4. For any other peaks eluting apart from the above mentioned relative retention, apply a response factor of 1.

In the chromatogram obtained with solution (2) the area of any individual peaks corresponding to hypoxanthine, inosine, 2'-deoxyinosine, 2',3'-didehydrodidanosine and didanosine acetate is not greater than 0.3 times the area of the principal peak obtained with solution (3) (0.3%). Any other impurity peak is not greater than 0.1 times the area of the principal peak obtained with solution (3) (0.1%). The sum of the areas of all peaks, other than the principal peak, is not greater than the area of the principal peak obtained with solution (3) (1.0%). Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (3) (0.05%).

Assay. Dissolve about 0.200 g, accurately weighted, in 50 ml glacial acetic acid R1 and titrate with perchloric acid (0.1 mol/l) VS as described under "Non-aqueous titration"; Method A (Vol. 1, p.131) determining the end point potentiometrically.

Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 23.62 mg of $C_{10}H_{12}N_4O_3$.

Tested impurities

- A. "Hypoxanthine" = 1,7-dihydro-6*H*-purin-6-one
- B. "Inosine" = 9-β-D-ribofuranosyl-1,9-dihydro-6*H*-purin-6-one
- C. "2'-Deoxyinosine" = 9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1,9-dihydro-6*H*-purin-6-one
- D. "2',3'-Didehydridanosine" = 9-[(2*R*,5*S*)-5-(hydroxymethyl)-2,5-dihydrofuran-2-yl]-1,9-dihydro-6*H*-purin-6-one; 9-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-1,9-dihydro-6*H*-purin-6-one
- E. "Didanosine acetate" = 9-[(2*R*,5*S*)-5-(acetyloxy)methyl]tetrahydrofuran-2-yl]-1,9-dihydro-6*H*-purin-6-one; 9-(5-*O*-acetyl-2,3-dideoxy-β-D-glycero-pentofuranosyl)-1,9-dihydro-6*H*-purin-6-one

Note: Other impurities will also be tested for detection by the methods described.

Reagents

Hypoxanthine R. 1,7-dihydro-6*H*-purin-6-one; C₅H₄N₄O.

A commercially-available reagent of suitable grade.

Description. A white, crystalline powder.

Solubility. Very slightly soluble in water, sparingly soluble in boiling water, soluble in dilute acids and in dilute alkali hydroxide solutions.

Melting point. Decomposes without melting at about 150 °C.

Thin-Layer Chromatography. Examine as prescribed in the monograph on mercaptopurine (Vol. 4, p.77-79); the chromatogram shows only one principal spot.

Inosine R. 9-β-D-ribofuranosyl-1,9-dihydro-6*H*-purin-6-one; C₁₀H₁₂N₄O₅.

A commercially-available reagent of suitable grade.

Description. A white, crystalline powder. Dihydrate, long rectangular plates from water, melting point = 90 °C. Anhydrous needles from 80% alcohol, decomposition 218 °C (rapid heating).

Solubility. Sparingly soluble in water.

Specific optical rotation. $[\alpha]_D^{18^\circ\text{C}} = -49.2^\circ$ (c = 0.9 in H₂O with c = concentration by volume, g/100 ml after optical rotation only); $[\alpha]_{\text{white}}^{20^\circ\text{C}} = -73^\circ$ (0.5 g + 2 ml NNaOH + 3 ml H₂O).

Silica gel for chromatography, octadecylsilyl, base-deactivated

A very finely divided silica gel, pretreated before the bounding of octadecylsilyl groups by careful washing and hydrolysing most of the superficial siloxane bridges to minimize the interaction with basic components.

Regulatory and Safety Action

Nimesulide temporarily suspended

Finland — The National Agency for medicines, together with the manufacturer, has decided to suspend the distribution, sale and supply of nimesulide (Nimed®) pending a review. Nimesulide is an anti-inflammatory analgesic approved for marketing in January 1998. It is indicated for transient pain, the treatment of pain associated with arthrosis, dysmenorrhoea and fever.

The decision followed reports of severe hepatic adverse reactions. By March 2003, 109 reports had been received by the Agency, 66 of which were of liver effects. Reports involved elevated liver enzymes in cases of hepatitis and isolated cases necessitating liver transplant.

Use of nimesulide is not forbidden, but patients are requested to contact their physician to ensure appropriate use. Any symptoms of liver dysfunction such as malaise, nausea, lack of appetite, abdominal pain or jaundice should be reported immediately.

Reference: Press Release. National Agency for Medicines. <http://www.nam.fi>, 6 February 2003.

Topiramate: revised prescribing information

United States of America/Canada — The manufacturer of topiramate (Topamax®) has updated the product information based on clinical trial and post-marketing experience in more than 2 million patients worldwide. Rare reports, primarily involving children, have been received of oligohidrosis (decreased sweating) and hyperthermia. Most cases have occurred in association with exposure to elevated environmental temperatures and/or vigorous activity, and children should be observed closely under these conditions. In the majority of patients, topiramate therapy has been continued. Proper hydration before and during activities such as exercise or exposure to warm temperatures is recommended.

As of February 2002, the rate for spontaneous postmarketing reports of all potential cases of oligohidrosis is approximately 35 per 1 000 000 patients treated and 1.6 per 1 000 000 patients treated for serious or medically significant oligohidrosis or its sequelae. It is generally recognized that postmarketing data are subject to substantial under-reporting.

Caution should be used when topiramate is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.

Patients, especially paediatric patients, should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather.

References

1. Undated letter from Ortho-McNeil Pharmaceutical. <http://www.fda.gov/medwatch>.
2. Letter from Janssen-Ortho dated 11 July 2003. <http://www.hc-sc.gc.ca>

Omalizumab for allergy-related asthma

United States of America — The Food and Drug Administration (FDA) has approved the first biotechnology product to treat patients with allergy-related asthma. Omalizumab (Xolair®), is a monoclonal antibody shown to be safe and effective for patients with moderate to severe allergy-related asthma inadequately controlled with inhaled corticosteroid treatments. In these patients, omalizumab has been shown to decrease the number of asthma exacerbations or episodes of airway narrowing that result in wheezing, breathlessness, and cough. The product is given as an injection under the skin.

As a second-line treatment, it is recommended when first-line treatments have failed; it is not approved for children under the age of 12 and is only for patients with moderate to severe, allergy-

related asthma. Only patients who have asthma caused by allergies — to be established by skin or blood test before treatment — can benefit from this new treatment.

The effectiveness of omalizumab was mainly assessed in two placebo-controlled studies of over 1000 adolescents and adults lasting six months. These patients all had persistent symptoms despite the use of inhaled corticosteroids. About 80–85% of patients treated with omalizumab had no exacerbation of their asthma symptoms compared to about 70–75% of placebo treated patients. During clinical trials, more patients treated with omalizumab developed a new or recurrent cancer (0.5%) compared to control patients (0.2%). The sponsor is planning long-term studies in an attempt to determine whether there is a relationship.

The other major safety concern was severe allergic reactions or anaphylaxis. Anaphylaxis occurred in three patients who all responded and recovered following medical treatment.

Reference: *FDA Talk Paper*, T03-49, 20 June 2003.

Co-packaged treatments for cerebrovascular events

United States of America — The Food and Drug Administration (FDA) has approved Pravigard PAC® (co-packaged pravastatin sodium and buffered aspirin tablets) for use when treatment is appropriate. Pravachol and buffered aspirin are indicated for reducing the occurrence of cardiovascular events, including death, myocardial infarction or stroke in patients with clinical evidence of cardiovascular and/or cerebrovascular disease. Patients should also be placed on a standard cholesterol-lowering diet.

Pravigard PAC® should not be taken by patients who have certain liver or kidney problems, women who are pregnant or planning to become pregnant, individuals less than 18 years of age or by individuals who are allergic to nonsteroidal anti-inflammatory (NSAID) medicines or any of the ingredients in Pravigard PAC®.

Possible serious side effects include muscle or liver damage, bleeding and stomach problems. Patients should report unexplained muscle pain or weakness, unusual bleeding, heartburn, nausea or vomiting, stomach pain or bowel movements or

stools that look like black tar. Liver function tests may be performed prior to initiation of treatment.

Reference: *FDA Talk Paper*, T03-51, 25 June 2003

OTC omeprazole approved for heartburn

United States of America — The Food and Drug Administration (FDA) has approved omeprazole (Prilosec OTC®), the first over-the-counter treatment for frequent heartburn.

Unlike the two classes of currently marketed over-the-counter heartburn treatments, antacids and acid reducers, omeprazole is indicated for the treatment of heartburn that occurs two or more days per week (frequent heartburn). It stops acid production at its source. Omeprazole is currently widely prescribed for frequent heartburn and other related but more serious problems that need the care of a physician. Omeprazole is not for people who have heartburn infrequently — one episode of heartburn a week or less — or for those who want immediate relief of heartburn.

Although side effects from omeprazole are not common they can include: headache, diarrhoea, constipation, upset stomach, vomiting, stomach pain, cough, cold symptoms, dizziness and rash.

Prescription-only omeprazole, first approved by FDA in 1989, will remain available for diseases that require diagnosis and supervision by a doctor, such as gastro-oesophageal reflux disease (GERD), inflammation of the oesophagus (oesophagitis) and ulcers.

Because of the safety studies being performed by the manufacturer, this product will have three years of over-the-counter exclusivity. Generic versions of the prescription product will not be able to market an OTC version until the marketing exclusivity has expired.

Reference: *FDA News*, P03-48. 20 June 2003.

Recombinant antihaemophilic factor licensed

United States of America — The Food and Drug Administration (FDA) has licensed a new recombinant DNA-derived clotting factor to treat

people with haemophilia A. This new anti-haemophilic human factor VIII product is the first produced without using additives derived from human or animal blood in the manufacturing process.

The new product, ADVATE® Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method (rAHF-PFM), is approved to prevent and control bleeding episodes or to prepare persons with haemophilia for surgery. It is produced by genetically engineered Chinese hamster ovary cells that have been altered to produce factor VIII.

Current factor VIII products (both plasma-derived and recombinant) are considered very safe as a result of many technological advances in the last two decades. These include viral inactivation and removal steps in manufacturing that are believed to effectively prevent transmission of hepatitis B, hepatitis C or HIV from plasma-derived products. These same procedures are considered effective to minimize any infectious risks from products made by DNA technology, which uses living cells. None of these products is reported to have transmitted HIV, hepatitis B or hepatitis C since 1987.

The first recombinant antihemophilic factor was approved in 1992. However, until now, all recombinant factor VIII products were made with blood-derived additives of human or animal origin, such as albumin. These additives were needed to keep the cells viable so they could make the factor VIII protein.

Reference: *FDA Talk Paper*, T03-55. 25 July 2003

New diabetes device approved

United States of America — The Food and Drug Administration (FDA) has cleared the first device for diabetics which integrates a glucose meter and insulin pump with a dose calculator. The new device could be the first step in the development of a fully automated glucose monitoring and insulin delivery system.

The product, made by Medtronic MiniMed, Inc., and Becton Dickinson, combines the Medtronic MiniMed Paradigm insulin pump® with a Becton Dickinson glucose monitor and facilitates data interchange between the two. It has additional circuitry and software modifications that allow it to transmit glucose values to the insulin pump and to transfer data between the insulin pump and a

personal computer running the appropriate Medtronic MiniMed® communications software. Since the glucose meter calculates and transmits information to the insulin pump automatically, it prevents the errors that can sometimes result when patients input this data manually. In addition, use of the integrated system is expected to make it more convenient for people to manage their diabetes.

FDA cleared the device for marketing based on safety and effectiveness of the separately marketed components and on reviews of the new device configuration, software, usability studies and electromagnetic interference compatibility testing conducted by the firms.

Reference: *FDA Talk Paper*, P03-49. 7 July 2003.

Recombinant somatropin approved for short stature

United States of America — The Food and Drug Administration (FDA) has approved a new indication for somatropin, rDNA origin, for injection (Humatrope®), a brand of growth hormone, for the long-term treatment of children with idiopathic short stature, also called non-growth hormone deficient short stature.

“Short stature” has been defined by the American Association of Clinical Endocrinologists and the Growth Hormone Research Society as height more than 2 standard deviations (SD) below the mean for age and sex. This corresponds to the shortest 2.3 percent of children. This new indication restricts therapy to children who are even shorter, specifically more than 2.25 SD below the mean for age and sex, or the shortest 1.2% of children.

Approval was based on two randomized, multi-centre trials, conducted in approximately 300 children with idiopathic short stature after excluding other causes, including growth hormone deficiency.

The pivotal trial was a randomized, double-blind study in 71 children aged 9–15 years. Patients received injections of either Humatrope® or placebo three times weekly until adult height was reached. Thirty-three patients contributed final height measurements after a mean treatment duration of 4.4 years. Mean final height of patients exceeded that of the placebo patients by approximately 1.5 inches.

In a second study, patients received one of three increasing doses in divided doses six times weekly. The average duration of treatment to final height was 6.5 years. Final height exceeded that predicted at the time of enrolment in the majority of patients, and by up to nearly four inches in some. In the high-dose group, mean final height exceeded mean height predicted at baseline by nearly three inches.

The safety profile in children with idiopathic short stature did not differ from that in children with other conditions for which growth hormone is indicated.

Various growth hormone products are currently indicated in children for short stature associated with growth hormone deficiency, chronic renal insufficiency, Turner syndrome, Prader-Willi syndrome, and in children born small for gestational age.

The manufacturer has advised FDA that it will not engage in direct-to-consumer advertising and will limit the marketing of this product for this new use to paediatric endocrinologists only to better ensure proper use in the indicated population. In addition, the manufacturer intends to tightly control distribution.

Reference: <http://www.fda.gov/medwatch> 30 May 2003.

Diagnostic test for West Nile virus

United States of America — The Food and Drug Administration (FDA) has approved the first test for use in the clinical laboratory diagnosis of West Nile virus infection. West Nile Virus IgM Capture ELISA® is intended for use in patients with clinical symptoms consistent with viral encephalitis/meningitis.

The new test works by detecting the levels of a particular type of antibody, IgM, to the disease in serum. IgM antibodies can be detected within the first few days of the onset of illness and can assist in the diagnosis of these patients.

The assay was evaluated using over 1000 patient sera tested at four different clinical sites. The test correctly identified antibody in 90–99% of cases. Because detection of antibody is not always specific in patients with acute viral infections, this test is considered presumptive and should be confirmed by more specific testing. Although the

test is a valuable aid in the diagnosis of West Nile virus encephalitis, due to similarities with other viruses in the same family, there is a need to confirm positive results by an additional test or by using the current CDC diagnostic guidelines.

West Nile virus is a mosquito-borne virus which first appeared in the United States in 1999. While the virus often presents as a mild infection that clears without further treatment, some patients develop severe infection resulting in neurological disease and even death. The disease is most prevalent during the peak mosquito season. Over the past several years, the geographic range of the virus as well as the number of new infections has expanded and now covers most of continental United States.

Reference: *FDA Talk Paper*, P03-51. 9 July 2003.

Etanercept for ankylosing spondylitis

United States of America — The Food and Drug Administration (FDA) has approved an application for etanercept (Enbrel®), a genetically-engineered protein, for a new indication for treatment of patients with active ankylosing spondylitis (AS), a chronic inflammatory disease affecting primarily the lower back and joints. Etanercept is also licensed for treatment of patients with rheumatoid arthritis, juvenile rheumatoid arthritis, and psoriatic arthritis.

The disease affects men more often than women. Symptoms of the disease may start in adolescence and are usually present by age 30. Patients often have lower back pain and stiffness, chest pain, joint pain and swelling, and tenderness due to inflammation. In some patients the disease can cause significant pain and disability for many years.

Etanercept binds to tumour necrosis factor (TNF), a naturally occurring protein in the body, and inhibits its action. TNF, promotes inflammation in the body and is found at elevated levels in the blood and certain tissues of patients with AS. It is believed that interference with TNF plays a role in the beneficial effects of etanercept for AS.

The major efficacy trial of etanercept for AS was a randomized, double-blind, placebo-controlled study of 277 patients. The study excluded patients with the most severe forms of AS. After six months of twice-weekly treatments, 58% of

patients who received etanercept showed significant improvement on a scale that measured pain, function, and inflammation compared to 23% who received a placebo.

In the study, the main side effects of etanercept were similar to those previously seen for this drug for other indications, including injection site reactions and upper respiratory infections. The approved labelling warns physicians about post-marketing reports of serious infections.

Etanercept should not be given to patients with any active infection, including chronic or localized infections. It also recommends that patients who develop a new infection should be monitored closely.

Reference: *FDA Talk paper*, T03-54 24 July 2003

Porfimer sodium approved for Barrett oesophagus

United States of America — The Food and Drug Administration (FDA) has approved porfimer sodium Injection (Photofrin®) for the ablation of precancerous lesions (high-grade dysplasia) in Barrett oesophagus patients who do not undergo surgery to remove the oesophagus (oesophagectomy).

Barrett oesophagus is a condition in which oesophagus lining is replaced by a type of tissue similar to that normally found in the intestine. Barrett oesophagus is estimated to affect about 700 000 adults in the United States. It is associated with the very common condition gastro-oesophageal reflux disease or GERD.

While Barrett oesophagus may cause no symptoms itself, a small number of people with this condition develop pre-cancerous lesions that progress to an often deadly type of cancer of the oesophagus called oesophageal adenocarcinoma.

Porfimer sodium is a photosensitizing agent used in photodynamic therapy (PDT), a treatment for some types of cancer. PDT is based on the discovery that photosensitizing agents can kill one-celled organisms when the organisms are exposed to a particular type of light. PDT destroys cancer cells through the use of a laser light in

combination with a photosensitizing agent. FDA first approved porfimer sodium in 1998.

The clinical study supporting this new use of Photofrin PDT® showed that patients were more likely to achieve complete reversal of their pre-cancerous lesions in Barrett oesophagus and had an 80% chance of being cancer-free. However, the effectiveness of Photofrin PDT® in reducing the long-term risk of oesophageal cancer has not been demonstrated.

Side effects include photosensitivity reactions and oesophageal strictures. Precautions should be taken to avoid exposure of skin and eyes to bright light.

Reference: *FDA Talk paper*, T03-60 4 August 2003

New drug approved for lowering cholesterol

United States of America — The Food and Drug Administration (FDA) has approved a new HMG-CoA reductase inhibitor, rosuvastatin (Crestor®), to lower cholesterol.

Rosuvastatin was approved based on multiple trials of at least 6 weeks' duration in which rosuvastatin treatment was compared to placebo and other marketed statins. In these trials, rosuvastatin reduced total-C, LDL-C, and TG and increased HDL-C with therapeutic response occurring within one week and maximum response seen at four weeks. Approximately 12 000 patients received rosuvastatin at different doses.

The most frequent side effects seen in patients treated with rosuvastatin included muscle aches, stomach pain, constipation, nausea, and weakness. In rare instances, severe muscle pain and muscle weakness resulting in kidney damage have been associated with statin drugs. If general muscle aches persist, patients should call their physician. Patients should be monitored for abnormalities of liver function before treatment, at 12 weeks following initial therapy and with any elevation of dose. Monitoring is recommended periodically thereafter.

Reference: *FDA Talk paper*, T03-6, 12 August 2003

Regulatory Challenges

Regulation of fixed-dose combination products

Internationally, there is an increasing trend to license fixed-dose combination products for the market. In less well-resourced countries, fixed-dose combination products (FDCs) hold a particular attraction in the treatment of communicable diseases such as tuberculosis, malaria and HIV because of both their lower cost and the reduced complexity of procurement and distribution. However, for a drug regulatory authority, a number of specific questions need to be addressed before applications to register FDCs can be licensed. Such issues include whether the combination is rational, or whether it will encourage inappropriate prescribing.

What is a fixed-dose combination?

The term fixed-dose combination product is synonymous with fixed-ratio combination product. Both terms refer to a product that contains two or more active ingredients. Because the product is of a defined composition, the two (or more) ingredients are present in a fixed ratio. Hence the term "fixed dose" or "fixed ratio" combination.

Such a product may be available in more than one strength, each of which may itself be a fixed dose combination and may contain different ratios of active ingredients. For example, Augmentin Duo Forte® tablets contain 850 mg of amoxicillin and 125 mg of clavulanic acid (a ratio of 6.8:1) whereas Augmentin Forte® tablets contain 500 mg of amoxicillin and 125 mg of clavulanic acid (a ratio of 4.0:1). Different ratios can be rational in particular circumstances.

Advantages of fixed-dose combinations

The presumed advantages of FDCs include:

- Drugs that are normally given in combination are more conveniently prescribed and consumed as an FDC.

- Better patient compliance is claimed (but see below).
- It is cheaper to purchase an FDC product than to purchase the products separately.
- The logistics of procurement and distribution are simpler (which can be especially important in remote areas).

Disadvantages of fixed-dose combinations

Critics of FDCs suggest that:

- FDCs discourage separate titration of each active ingredient. This is a particular problem when both of the active ingredients require dose titration. Indeed, it can be argued that the very existence of an FDC discourages adjustment of doses to the patient's needs (if that is appropriate for the combination in question).
- When the active ingredients in question have different pharmacokinetics and/or pharmacodynamics, an FDC may not be appropriate.
- Unless both of the active ingredients are available as separate entities, FDCs encourage polypharmacy irrespective of whether it is appropriate for a particular patient.

Patient compliance

There is a general assumption that FDCs will achieve better patient compliance than prescription of the same actives in separate products. This belief would appear to be intuitive rather than evidence-based. A recent Cochrane review (1) examined available evidence as to the value of interventions in improving patient adherence to medication schedules. In terms of dose schedules, the major factor affecting patient compliance appears to be the number of occasions on which a patient takes medication in a day, with adherence to regime decreasing for three or more dosing events per day. The effect on compliance of using FDCs rather than two or more single entity products appears not to have been studied (2).

Text prepared by Susan Walters, PhD, BPharm, Consultant, Australia.

Cost and logistics

Minimizing costs and simplifying the logistics of procurement and distribution of complex antimicrobial regimens are legitimate objectives in achieving public health outcomes in less well-resourced nations. FDCs can usefully contribute to both of these elements, but only if they do not compromise therapeutic outcomes.

Considerations for drug regulation

WHO has made the following comments about FDCs. "New fixed-ratio combination products are regarded as new drugs in their own right. They are acceptable only when (a) the dosage of each ingredient meets the requirements of a defined population group, and (b) the combination has a proven advantage over single compounds administered separately in terms of therapeutic effect, safety or compliance. They should not be treated as generic versions of single-component products" (3, 4).

A busy prescriber may be tempted to select an FDC when patient titration of the individual active ingredients would be the better course. Combinations of anti-hypertensives might be an example. The busy prescriber may not have read the prescribing information for the FDC to enable him/her to determine the circumstances in which it is appropriate therapy, and the circumstances in which separate titration of the active ingredients

would be in the patient's interest. This is an example of what might be described as inappropriate prescribing.

Similarly, prescribing of an opiate in combination with paracetamol only because it is an available FDC could be described as inappropriate. If the patient needs high-dose analgesic therapy, this combination might contribute to hepatotoxicity via the paracetamol component. However, there certainly may be circumstances in which the FDC is an appropriate combination. A number of regulatory authorities have published guidelines that attempt to establish the principles that define those circumstances. The following table lists regulatory guidelines on the subject of fixed-dose combination products.

References

- Haynes, R.B., McDonald, H., Garg, A.X. Interventions for helping patients to follow prescriptions for medications. *Cochrane Library*, Update Software, Issue 2. Oxford, England. 2002.
- Haynes, R.B. Personal communication, 2003.
- World Health Organization. The Use of Essential Drugs. Seventh report of the WHO Expert Committee. *Technical Report Series*, No. 867 (1997).
- World Health Organization. *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: A manual for a Drug Regulatory Authority*. WHO/DMP/IRGS/98.5 (1998).

Guidelines on fixed-dose combination products

Title, publisher & date	Notes
<p>United States of America</p> <p>Fixed-combination prescription drugs for humans. Food and Drug Administration. FDA 21CFR300.50 (Revised 1 April 2003). Federal Register, on: http://www.accessdata.fda.gov/scripts/cdrh/cfd</p> <p>Conjugated estrogens, USP-LC-MS method for both qualitative chemical characterization and documentation of qualitative pharmaceutical equivalence. FDA June 2000 (draft). http://www.fda.gov/cder/guidance/3668dft.pdf</p>	<p>Approx 250 words. In terms of safety and efficacy, describes the circumstances in which active ingredients may be combined in an FDC.</p> <p>Seven pages. This guideline relates only to conjugated estrogens from a biological source, normally pregnant mares' urine, which contains multiple estrogens. There have been difficulties in preparing generic equivalents of this type of product. The guideline specifies how chemical equivalence can be demonstrated.</p>

Title, publisher & date	Notes
<p>Estrogen & Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation. FDA January 2003 (draft). http://www.fda.gov/cder/guidance/5412dft.pdf</p> <p>National Uniformity for Nonprescription Drugs – Ingredient Listing for OTC Drugs FDA, April 1998 – Procedural guidance. http://www.fda.gov/cder/guidance/2219fnl.pdf</p> <p>Enforcement Policy on Marketing OTC Combination Products. FDA, March 1998 http://www.fda.gov/cder/guidance/old001fn.pdf</p> <p>(a)(4)(iv) in: Procedures for Classifying OTC Drugs as Generally Recognized as Safe and Effective and not Misbranded, and for Establishing Monographs. FDA 21CFR330.10 in Federal Register, January 2002 http://www.accessdata.fda.gov/scripts/cdrh/cfd</p> <p>General Guidelines on OTC Combination Products. In Federal Register, March 1998. http://www.fda.gov/cder/guidance/old002fn.pdf</p>	<p>Ten pages. This guideline is not restricted to estrogens from a biological source. Approval will be based on two criteria:</p> <ul style="list-style-type: none"> • That each component contributes to safety and efficacy as defined in 21CFR300.50, and • The FDC contains the lowest effective dose of each of the active ingredients for their respective labelled indication. <p>Two pages. Cross-refers to proposed and existing legislation. Defines a standardized format of labelling of active and inactive ingredients, including nomenclature, doses and order of listing of ingredients.</p> <p>Three pages. Describes possible action by sponsors following a recommendation as to regulatory action after review of a category of OTC product and, possibly, establishment of a monograph.</p> <p>Approx 80 words. In terms of safety and efficacy, describes the circumstances in which active ingredients may be combined in an OTC product. Specifies there must be adequate directions for use and warnings against unsafe use.</p> <p>Two pages. Cross-refers to (a)(4)(iv) in FDA 21CFR330.10 (see above) and further defines the circumstances (safety and efficacy) in which two or more active ingredients may be combined in an OTC product. Specifies that OTC monographs will list permitted combinations (in the context of GRAS reviews of OTC products and establishment of monographs).</p>
<p>Australia</p> <p>Fixed-combination products in: Australian Guidelines for the Registration of Drugs. Vol. 1. Therapeutic Goods Administration (TGA) 1994. http://www.health.gov.au/tga/docs/html/agrd1.htm</p>	<p>Approx 250 words. Discusses justification of the combination in terms of either pharmacodynamics or demonstrated therapeutic effect.</p>
<p>International Conference on Harmonization (ICH)/ Europe</p> <p>Fixed combination products in ICH principles document for clinical evaluation of new antihypertensive drugs. Part 6 (Draft). ICH/CPMP/541/00 (draft). http://www.ich.org/pdf/ICH/e12.pdf</p>	<p>Approx 250 words. Describes two experimental designs for safety and efficacy studies on FDCs of antihypertensives, namely factorial studies and studies in patients who have failed to respond adequately to each of the drugs given separately.</p>

Title, publisher & date	Notes
<p>Fixed combinations in Note for guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension. Part 7. CPMP Nov 1997 – CPMP/EWP/238/96 Rev1 http://www.emea.eu.int/pdfs/human/ewp/023895en.pdf</p> <p>Fixed-Combination Medicinal Products. CPMP April 1996 — CPMP/EWP/240/95, III/5773/94 (formerly known as: Testing and Licensing Criteria for Fixed Combination Medicinal Products). http://www.emea.eu.int/pdfs/human/ewp/024095en.pdf</p> <p>Fixed combination products in: Note for Guidance on the Investigation of Bioavailability & Bioequivalence. 5.1.5 CPMP July 2001. CPMP/EWP/QWP/1401/98 http://www.emea.eu.int/human/ewp/140198en.pdf</p> <p>Note for Guidance on Fixed Combinations of Herbal Medicinal Products with Long-Term Marketing Experience. Guidance to Facilitate Mutual Recognition and Use of Bibliographic Data. CPMP, January 1999. EMEA/HMPWP/15/99. http://www.emea.eu.int/pdfs/human/hmpwp/001599en.pdf</p> <p>The ratio and/or fixed content of one component of a combination drug product (IV.3). In: Points to Consider on Pharmacokinetics and Pharmacodynamics in the Development of Antibacterial Medicinal Products. CPMP, July 2000. CPMP/EWP/2655/99 http://www.emea.eu.int/pdfs/human/ewp/265599en.pdf</p>	<p>Three pages that:</p> <ul style="list-style-type: none"> • describe the circumstances (in terms of safety and efficacy) in which FDCs may be acceptable in the therapy of hypertension, and • provide advice on their clinical development as first or second-line therapy. <p>NB: The section on FDCs in this guideline is different to the draft ICH guideline on new antihypertensives.</p> <p>Four pages that:</p> <ul style="list-style-type: none"> • require justification of the particular combination • give examples of circumstances (safety and efficacy) in which FDCs may be acceptable • describe principles that define acceptable indications • require consideration of possible pharmacokinetic and pharmacodynamic interactions • require evidence as to safety and efficacy (allowing bibliographic data as supportive evidence in certain circumstances) • require evidence on safety and efficacy of the doses selected. <p>Also applicable to a new chemical substance which dissociates in vivo into two well known active substances. Substances having a critical dosage range or a narrow therapeutic index are unlikely to be suitable for inclusion in fixed combinations.</p> <p>Approx 50 words. States that FDCs should in general be assessed as to the bioavailability and bioequivalence of the individual active ingredients either separately (in the case of a new combination) or as an existing combination. Studies should be designed to detect any pharmacokinetic drug-drug interaction.</p> <p>Three pages. Very similar content to Fixed-Combination Medicinal Products, CPMP, April 1996. CPMP/EWP/240/95, III/5773/94 (above). Requirements in relation to safety aspects and therapeutic data cross-refer to other guidelines on herbal medicinal products. Possible pharmacokinetic and pharmacodynamic interactions must be discussed as far as data are available.</p> <p>Seven pages. This guideline discusses the relationship between plasma concentration/time profiles and clinical efficacy. Selection of a suitable ratio of doses for FDCs is discussed in Part IV B (approx 100 words).</p>

ATC/DDD Classification (final)

The following final anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 23–24 October 2002. They came into force on 1 March 2003 and are included in the January 2004 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, e-mail: whocc@nmd.no.

ATC level	INN/Common name	ATC code
<i>New ATC level codes (other than 5th level):</i>		
	Direct thrombin inhibitors	B01AE
	Other anterior pituitary hormones and analogues	H01AX
	Prostaglandin analogues	S01EE
<i>New ATC 5th level codes:</i>		
	adalimumab	L04AA17
	adefovir dipivoxil	J05AF08
	afelimomab	L04AA16
	alefacept	L04AA15
	aluminium diacetate	D10AX05
	argatroban	B01AE03
	benidipine	C08CA15
	beraprost	B01AC19
	bimatoprost	S01EE03
	carbon dioxide	V03AN02
	ciclesonide	R03BA08
	combinations	D06AX30
	docosanol	D06BB11
	eflornithine	D11AX16
	eprosartan and diuretics	C09DA02
	ertapenem	J01DH03
	etilevodopa and decarboxylase inhibitor	N04BA06
	etoricoxib	M01AH05
	everolimus	L04AA18
	fasudil	C04AX32
	frovatriptan	N02CC07
	glutaral	D08AX09
	gusperimus	L04AA19
	helium	V03AN03
	insulin aspart	A10AD05
	lanthanum carbonate	V03AE03
	levodopa, decarboxylase inhibitor and COMT inhibitor	N04BA03
	levofloxacin	S01AX19
	lofexidine	N07BC04

ATC level	INN/Common name	ATC code
	lovastatin, combinations	C10AA52
	melagatran	B01AE04
	melevodopa	N04BA04
	melevodopa and decarboxylase inhibitor	N04BA05
	methotrexate	L04AX03
	moxonidine and diuretics	C02LC05
	nitrogen	V03AN04
	oxygen	V03AN01
	pegvisomant	H01AX01
	pimecrolimus	D11AX15
	polygeline	B05AA10
	rifampicin, pyrazinamide and isoniazid	J04AM05
	rifampicin, pyrazinamide, ethambutol and isoniazid	J04AM06
	rifapentin	J04AB05
	telmisartan and diuretics	C09DA07
	travoprost	S01EE04

ATC codes changes:

Previous:	desirudin	B01AX02
New:	desirudin	B01AE01
Previous:	latanoprost	S01EX03
New:	latanoprost	S01EE01
Previous:	lepirudin	B01AX03
New:	lepirudin	B01AE02
Previous:	unoprostone	S01EX04
New:	unoprostone	S01EE02

ATC name changes:

Previous:	ethambutol, combinations	
New:	ethambutol and isoniazid	J04AM03
Previous:	rifampicin, combinations	
New:	rifampicin and isoniazid	J04AM02
Previous:	somatropin and analogues	
New:	somatropin and somatropin agonists	H01AC
Previous:	streptomycin, combinations	
New:	streptomycin and isoniazid	J04AM01
Previous:	thioacetazone, combinations	
New:	thioacetazone and isoniazid	J04AM04

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
anakinra	0.1	g	P	L04AA14
bosentan	0.25	g	O	C02KX01
dutasteride	0.5	mg	O	G04CB02
ertapenem	1	g	P	J01DH03
etoricoxib	60	mg	O	M01AH05
fentanyl	0.6	mg	SL	N02AB03
ferric oxide dextran complex	0.1	g Fe ³⁺	P	B03AC06

INN/common name	DDD	Unit	Adm.R	ATC code
fondaparinux	2.5	mg	P	B01AX05
frovatriptan	2.5	mg	O	N02CC07
fulvestrant	8.3	mg	P	L02BA03
gatifloxacin	0.4	g	O, P	J01MA16
glatiramer acetate	20	mg	P	L03AX13
lofexidine	1.4	mg	O	N07BC04
memantine	20	mg	O	N06DX01
miglustat	0.3	g	O	A16AX06
mometasone	0.4	mg	Inhal.powder	R03BA07
octreotide	0.7	mg	P	H01CB02
peginterferon alfa-2a	26	mcg	P	L03AB11
risperidone	1.8	mg	P depot	N05AX08
tenecteplase	40	mg	P	B01AD11
tenofovir disoproxil	0.245	g	O	J05AF07
tiotropium bromide	18	mcg	Inhal.powder	R03BB04
voriconazole	0.4	g	O, P	J02AC03
ziprasidone	40	mg	P	N05AE04

Change of DDDs:

INN/common name	Previous DDD	Unit	Adm.R	New DDD	Unit	Adm.R	ATC code
levofloxacin	0.25	g	O, P	0.5	g	O, P	J01MA12

ATC/DDD Classification (temporary)

The following temporary anatomical therapeutic chemical (ATC) classifications, defined daily doses (DDDs) and alterations were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 26 – 27 May 2003. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, e-mail: whocc@nmd.no before 15 September 2003. If no objections are received before this date, the new ATC codes and DDDs will be considered final and be included in the January 2004 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

ATC level	INN/Common name	ATC code
<i>New ATC 5th level codes:</i>		
	atomoxetine	N06BA09
	bemiparin	B01AB12
	bortezomib	L01XX32
	celecoxib	L01XX33
	combinations	B02BC30
	dextriferron	B03AD04
	drospirenone and estrogen	G03FA17
	efalizumab	L04AA21
	emtricitabine	J05AF09
	epinastine	S01GX10
	gemtuzumab	L01XC05
	levosulpiride	N05AL07
	lumiracoxib	M01AH06
	metformin and rosiglitazone	A10BD03
	minocycline	A01AB23
	nesiritide	C01DX19
	norelgestromin and estrogen	G03AA13
	solifenacin	G04BD08
	sulfadiazine and tetroxoprim	J01EE06
	triclabendazole	P02BX04
	trimegestone and estrogen	G03FA16
<i>ATC code changes</i>		
Previous:	budesonide	H02AB16
New:	budesonide	A07EA06
Previous:	tropium	A03AB20
New:	tropium	G04BD09

ATC name changes:

	ATC level	ATC code
Previous:	Biguanides and sulfonamides in combination	
New:	Combinations of oral blood glucose lowering drugs	A10BD
Previous:	Corticosteroids for local use	
New:	Corticosteroids acting locally	A07EA
Previous:	Psychostimulants and nootropics	
New:	Psychostimulants, agents used for ADHD and nootropics	N06B

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
adefovir dipivoxil	10	mg	O	J05AF08
alprostadil	0.5	mg	P	C01EA01
bemiparin	2.5	TU	P	B01AB12*
clarithromycin	1	g	P	J01FA09
disulfiram	0.2	g	O	N07BB01
drotrecogin alfa (activated)	40	mg	P	B01AD10
eptifibatide	0.2	g	P	B01AC16
ezetimibe	10	mg	O	C10AX09
imiglucerase	300	U	P	A16AB02
minocycline	1	mg	O	A01AB23*
oseltamivir	0.15	g	O	J05AH02
parecoxib	40	mg	P	M01AH04
pegfilgrastim	0.3	mg	P	L03AA13
pegvisomant	10	mg	P	H01AX01
procaine penicillin	0.6	g	P	J01CE09
rosuvastatin	10	mg	O	C10AA07
tadalafil	10	mg	O	G04BE08
teriparatide	20	mcg	P	H05AA02
valdecoxib	10	mg	O	M01AH03
varidenafil	10	mg	O	G04BE09

* Temporary ATC code

Change of DDDs

INN/common name	Previous DDD	Unit	Adm.R	New DDD	Unit	Adm.R	ATC code
bezitramide	10	mg	O	15	mg	O	N02AC05
galantamine	24	mg	O	16	mg	O	N06DA04
hydromorphone	4	mg	O	20	mg	O	N02AA03
leflunomide	15	mg	O	20	mg	O	L04AA13
oxycodone	30	mg	O	75	mg	O	N02AA05
repaglinide	6	mg	O	4	mg	O	A10BX02
rofecoxib	12.5	mg	O	25	mg	O	M01AH02

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 (1–85) and Recommended (1–45) International Nonproprietary Names can be found in *Cumulative List No. 10, 2002* (available in CD-ROM only). The statements indicating action and use are based largely on information supplied by the manufacturer. This information is merely meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature, these descriptors will neither be revised nor included in the Cumulative Lists of INNs.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Il est notifié que, conformément aux dispositions de l'article 3 de la Procédure à suivre en vue 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 (1–85) et recommandées (1–45) dans la *Liste récapitulative No. 10, 2002* (disponible sur CD-ROM seulement). Les mentions indiquant les propriétés et les indications des substances sont fondées sur les renseignements communiqués par le fabricant. Elles ne visent qu'à donner une idée de l'utilisation potentielle des nouvelles substances au moment où elles sont l'objet de propositions de DCI. L'OMS n'est pas en mesure de confirmer ces déclarations ni de faire de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations ne figureront pas dans les listes récapitulatives de DCI.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

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

Las listas de Denominaciones Comunes Internacionales Propuestas (1–85) y Recomendadas (1–45) se encuentran reunidas en *Cumulative List No. 10, 2002* (disponible sólo en CD-ROM). Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deben incluirse en las listas recapitulativas de DCI.

Proposed International Nonproprietary Names: List 89

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 89 Proposed INN not later than 31 December 2003**.

Dénominations communes internationales proposées: Liste 89

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 89 de DCI Proposées le 31 Décembre 2003 au plus tard**.

Denominaciones Comunes Internacionales Propuestas: Lista 89

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 89 de DCI Propuestas el 31 Diciembre 2003 a más tardar**.

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

adargileukinum alfa adargileukin alfa

[88-arginine]interleukin 2 (human clone pTIL2-21a) (partly glycosylated)

immunomodulator

adargileukine alfa

[88-arginine]interleukine 2 humaine (clone pTIL2-21a) (en partie glycosylée)

immunomodulateur

adargileukina alfa

[88-arginina]interleukina 2 humana (clon pTIL2-21a) (parcialmente glicosilada)

inmunomodulador

C₆₉₅H₁₁₂₄N₁₈₀O₂₀₂S₇ (peptide) 250710-65-7

APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLTRML
TFKFYMPKKA TELKHLQCLE EELKPLEEVL NLAQSKNFHL
RPRDLISRIN VIVLELKGSE TTFMCEYADE TATIVEFLNR
WITFCQSIIS TLT

alamifovirum
alamifovir

bis(2,2,2-trifluoroethyl) [(2-{2-amino-6-[(4-methoxyphenyl)sulfanyl]-9H-purin-9-yl}ethoxy)methyl]phosphonate

antiviral

alamifovir

[[2-{2-amino-6-[(4-méthoxyphényl)sulfanyl]-9H-purin-9-yl]éthoxy)méthyl]phosphonate de bis(2,2,2-trifluoroéthyle)

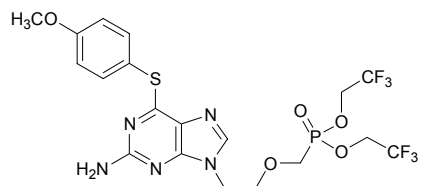
antiviral

alamifovir

[(2-{2-amino-6-[(4-metoxifenil)sulfanil]-9H-purin-9-il}etoxi)metil]fosfonato de bis(2,2,2-trifluoroetilo)

*antiviral*C₁₉H₂₀F₆N₅O₅PS

193681-12-8



aprinocarsenum

aprinocarsen

2'-deoxy-*P*-thioguanylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxyadenosine

antineoplastic

aprinocarsen

2'-désoxy-*P*-thioadénylyl-(5'→3')-2'-désoxy-*P*-thiocytidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-désoxy-*P*-thioguanylyl-(5'→3')-2'-désoxy-*P*-thioadénylyl-(5'→3')-2'-désoxy-*P*-thioguanylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-désoxy-*P*-thioguanylyl-(5'→3')-2'-désoxy-*P*-thioguanylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-désoxy-*P*-thiocytidylyl-(5'→3')-2'-désoxy-*P*-thioguanylyl-(5'→3')-2'-désoxy-*P*-thiocytidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-désoxy-*P*-thiocytidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-désoxyguanosine

antinéoplasique

aprinocarseno

2'-desoxi-*P*-tioadenilil-(5'→3')-2'-desoxi-*P*-tiocitidilil-(5'→3')-*P*-tiotimidilil-(5'→3')-*P*-tiotimidilil-(5'→3')-*P*-tiotimidilil-(5'→3')-2'-desoxi-*P*-tioguanilil-(5'→3')-2'-desoxi-*P*-tioadenilil-(5'→3')-2'-desoxi-*P*-tioguanilil-(5'→3')-*P*-tiotimidilil-(5'→3')-2'-desoxi-*P*-tioguanilil-(5'→3')-*P*-tiotimidilil-(5'→3')-2'-desoxi-*P*-tioguanilil-(5'→3')-*P*-tiotimidilil-(5'→3')-2'-desoxi-*P*-tiocitidilil-(5'→3')-2'-desoxi-*P*-tioguanilil-(5'→3')-2'-desoxi-*P*-tiocitidilil-(5'→3')-*P*-tiotimidilil-(5'→3')-2'-desoxi-*P*-tiocitidilil-(5'→3')-*P*-tiotimidilil-(5'→3')-*P*-tiotimidilil-(5'→3')-2'-desoxiguanosina

*antineoplásico*C₁₉₆H₂₄₉N₆₈O₁₀₅P₁₉S₁₉

151879-73-1

belimumabum

belimumab

immunoglobulin G1, anti-(human cytokine BAFF) (human monoclonal LymphoStat-B heavy chain), disulfide with human monoclonal LymphoStat-B λ -chain, dimer

immunomodulator

bélimumab

immunoglobuline G1, anti-(cytokine BAFF humaine) ; dimère du disulfure entre la chaîne lourde et la chaîne λ de l'anticorps monoclonal humain LymphoStat-B

immunomodulateur

belimumab

immunoglobulina G1, anti-(citoquina BAFF humana) ; dímero del disulfuro entre la cadena pesada y la cadena λ del anticuerpo monoclonal humano LymphoStat-B

inmunomodulador

356547-88-1

cantuzumabum mertansinum
cantuzumab mertansine

immunoglobulin G1, anti-(mucin CanAg) (human-mouse monoclonal C242 heavy chain), disulfide with human-mouse monoclonal C242 light chain, dimer, conjugate at the 6-amino groups of four lysine residues forming an amide bond with (4*RS*)-4-[[3-[[[(1*S*)-2-[[[(1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,20*R*,21*S*)-11-chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.1^{10,14}.0^{3,5}]]hexacos-10,12,14(26),16,18-pentaen-6-yl]oxy]-1-methyl-2-oxoethyl]=methylamino]-3-oxopropyl]disulfanyl]pentanoyl groups

treatment of tumors that express C242 antigen

cantuzumab mertansine

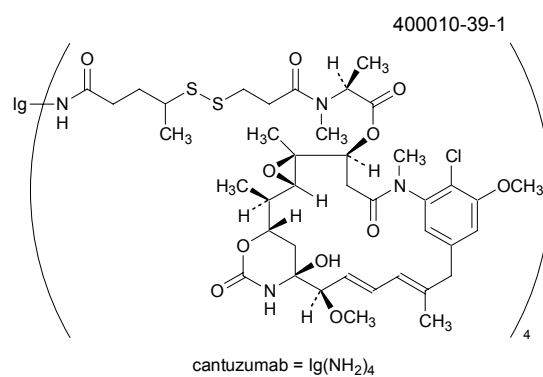
immunoglobuline G1, anti-(mucine CanAg) ; dimère du disulfure entre la chaîne lourde et la chaîne légère de l'anticorps monoclonal de souris C242 humanisé dont les groupes 6-amino de quatre lysines sont amidifiés par l'acide (4*RS*)-4-[[3-[[[(1*S*)-2-[[[(1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,20*R*,21*S*)-11-chloro-21-hydroxy-12,20-diméthoxy-2,5,9,16-tétraméthyl-8,23-dioxa-4,24-dioxa-9,22-diazatétracyclo[19.3.1.1^{10,14}.0^{3,5}]]hexacos-10,12,14(26),16,18-pentaén-6-yl]oxy]-1-méthyl-2-oxoéthyl]=méthylamino]-3-oxopropyl]disulfanyl]pentanoïque

antitumoral spécifique des cellules exprimant l'antigène C242

cantuzumab mertansina

inmunoglobulina G1, anti-(mucina CanAg) ; dímero del disulfuro entre la cadena pesada y la cadena ligera del anticuerpo monoclonal humanizado de ratón C242 en el que los grupos 6-amino de cuatro lisinas están amidificados por ácido (4*RS*)-4-[[3-[[[(1*S*)-2-[[[(1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,20*R*,21*S*)-11-cloro-21-hidroxi-2,5,9,16-tetrametil -12,20-dimetoxi-4,24-dioxa-8,23-dioxa-9,22-diazatetracyclo[19.3.1.1^{10,14}.0^{3,5}]]hexacos-10,12,14(26),16,18-pentaen-6-il]oxil]-1-metil-2-oxoetil]metilamino]-3-oxopropil]disulfanyl]pentanoico

antitumoral específico de las células que expresan el antígeno C242



cimicoxibum

cimicoxib

4-[4-chloro-5-(3-fluoro-4-methoxyphenyl)-1*H*-imidazol-1-yl]benzenesulfonamide*cyclooxygenase-2 inhibitor*

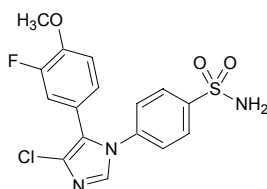
cimicoxib

4-[4-chloro-5-(3-fluoro-4-méthoxyphényl)-1*H*-imidazol-1-yl]benzènesulfonamide*anti-inflammatoire*

cimicoxib

4-[4-cloro-5-(3-fluoro-4-metoxifenil)-1*H*-imidazol-1-il]bencenosulfonamida*inhibidor de la ciclooxigenasa-2*C₁₆H₁₃ClFN₃O₃S

265114-23-6

**dabuzalgronum**

dabuzalgron

N-[6-chloro-3-[(4,5-dihydro-1*H*-imidazol-2-yl)methoxy]-2-methylphenyl]methanesulfonamide*α₁-adrenoreceptor agonist*

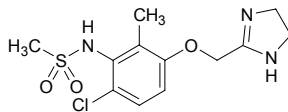
dabuzalgron

N-[6-chloro-3-[(4,5-dihydro-1*H*-imidazol-2-yl)méthoxy]-2-méthylphényl]méthanesulfonamide*agoniste α₁-adrénergique*

dabuzalgrón

N-[6-cloro-3-[(4,5-dihidro-1*H*-imidazol-2-il)metoxi]-2-metilfenil]metanosulfonamida*agonista de los receptores α₁-adrenérgicos*C₁₂H₁₆ClN₃O₃S

219311-44-1



dacinostat
dacinostat

(2*E*)-*N*-hydroxy-3-[4-((2-hydroxyethyl)[2-(1*H*-indol-3-yl)ethyl]amino)methyl]phenyl]propenamide

antitumour agent, inhibitor of histone deacetylase

dacinostat

(2*E*)-*N*-hydroxy-3-[4-[(2-hydroxyéthyl)[2-(1*H*-indol-3-yl)éthyl]amino]méthyl]phényl]prop-2-énamide

antitumoral, inhibiteur de l'histone désacétylase

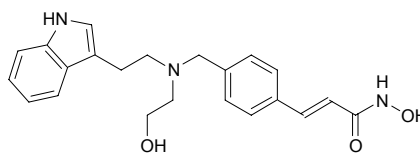
dacinostat

(2*E*)-*N*-hidroxi-3-[4-((2-hidroxietil)[2-(1*H*-indol-3-il)etil]amino)metil]fenil]propenamida

antitumoral, inhibidor de desacetilasa de histonas

C₂₂H₂₅N₃O₃

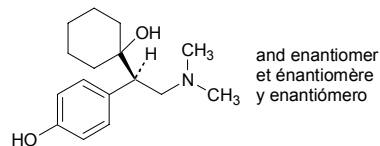
404951-53-7



deligoparinum natricum deligoparin sodium	sodium salt of depolymerised heparin obtained by a controlled chemical process based on generation of free radicals by means of metal ions and hydrogen peroxide. The heparin starting material is obtained from porcine intestinal mucosa. The process results in oligosaccharide fragments of heparin of varying lengths. The average relative molecular mass is about 3200 Daltons, ranging from 2250 to 3850 Daltons. The degree of sulfation is approximately 2.5 sulfate residues per disaccharide unit.
	<i>anticoagulant</i>
déligoparine sodique	sel de sodium d'héparine de basse masse moléculaire obtenue par dépolymérisation à l'aide de radicaux libres (générés par des ions métalliques et du peroxyde d'hydrogène) d'héparine de muqueuse intestinale de porc. La majorité des composants présentent une structure acide 2-O-sulfo- α -D-glucopyranosuronique à l'extrémité non réductrice et une structure 2-désoxy-6-O-sulfo-2-(sulfoamino)-D-glucopyranose à l'extrémité réductrice de leur chaîne ; la masse moléculaire relative moyenne est voisine de 3200 (2250 à 3850) ; le degré de sulfatation est voisin de 2,5 par unité disaccharide.
	<i>anticoagulant</i>
deligoparina sódica	sal sódica de una heparina de baja masa molecular que se obtiene de la heparina de la mucosa intestinal porcina por despolimerización por radicales libres, generados por iones metálicos y peróxido de hidrógeno; la mayoría de los componentes tienen una estructura de ácido 2- O -sulfo- α -D-glucopiranosurónico en el extremo no-reductor de la cadena y una estructura 2-desoxy-6-O-sulfo-2-(sulfoamino)-D-glucopiranososa en el reductor; la masa molecular media oscila entre 2250 y 3850, con un valor característico de unos 3200; el grado de sulfatación es alrededor de 2,5 por unidad de disacárido.
	<i>anticoagulante</i>
	9041-08-1
desvenlafaxinum desvenlafaxine	4-[(1RS)-2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenol
	<i>antidepressant</i>
dèsvenlafaxine	4-[(1RS)-2-(diméthylamino)-1-(1-hydroxycyclohexyl)éthyl]phénol
	<i>antidépresseur</i>
desvenlafaxina	4-[(1RS)-2-(dimetilamino)-1-(1-hidroxiciclohexil)etil]fenol
	<i>antidepresivo</i>

C₁₆H₂₅NO₂

93413-62-8

**dibotermine alfa**
dibotermine alfa

human recombinant bone morphogenic protein-2 (hrBMP-2)

growth factor

dibotermine alfa

protéine-2 humaine recombinante morphogénique de l'os (PMOrh-2)

facteur de croissance

dibotermine alfa

proteína-2 humana recombinante morfogénica de hueso (PMOrh-2)

factor de crecimiento[C₅₇₁H₈₈₆N₁₆₀O₁₆₄S₉]₂

246539-15-1

QAKHKQRKRL KSSCKRHPLY VDFSDVGWND WIVAPPGYHA
FYCHGECFPF LADHLNSTNH AIVQTLVNSV NSKIPKACCV
PTELSAISML YLDENEKVVL KNYQDMVVEG CGCR

diquafosol
diquafosolP¹,P⁴-bis(5'-uridylyl) tetrahydrogen tetraphosphate*P2Y₂ receptor agonist*

diquafosol

uridine(5')tétraphospho(5')uridine

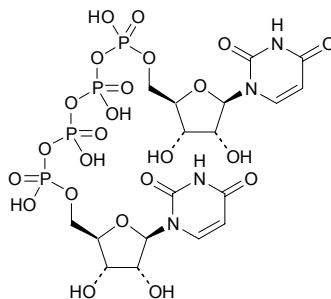
agoniste des récepteurs P2Y₂

diquafosol

tetrahidrógenotetrafosfato de P¹,P⁴-bis(5'-uridilo)*agonista de los receptores P2Y₂*

C₁₈H₂₆N₄O₂₃P₄

59985-21-6



disermolidum
disermolide

(3Z,5S,6S,7S,8R,9S,11Z,13S,14S,15S,16Z,18S)-
8,14,18-trihydroxy-19-[(2S,3R,4S,5R)-4-hydroxy-3,5-dimethyl-
6-oxotetrahydro-2H-pyran-2-yl]-5,7,9,11,13,15-
hexamethylnonadeca-1,3,11,16-tetraen-6-yl carbamate

antineoplastique

disermolide

carbamate de (1S,2S,3R,4S,6Z,8S,9S,10S,11Z,13S)-3,9,13-
trihydroxy-14-[(2S,3R,4S,5R)-4-hydroxy-3,5-diméthyl-
6-oxotétrahydro-2H-pyran-2-yl]-2,4,6,8,10-pentaméthyl-1-[(1S,2Z)-
1-méthylpenta-2,4-diényl]tétradéca-6,11-diényl

antinéoplasique

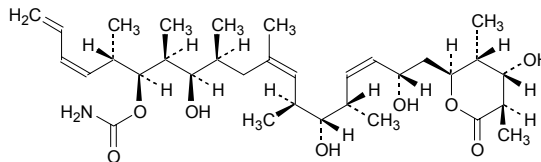
disermolida

carbamato de (3Z,5S,6S,7S,8R,9S,11Z,13S,14S,15S,16Z,18S)-
8,14,18-trihidroxi-19-[(2S,3R,4S,5R)-4-hidroxi-3,5-dimetil-
6-oxotetrahidro-2H-piran-2-il]-5,7,9,11,13,15-hexametilnonadeca-
1,3,11,16-tetraen-6-ilo

antineoplásico

C₃₃H₅₅NO₈

127943-53-7



elvucitabinum

elvucitabine

4-amino-5-fluoro-1-[(2*S*,5*R*)-5-(hydroxyméthyl)-2,5-dihydro-2-furyl]pyrimidin-2(1*H*)-one*antiviral*

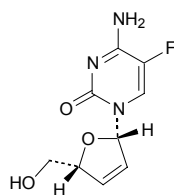
elvucitabine

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

elvucitabina

4-amino-5-fluoro-1-[(2*S*,5*R*)-5-(hidroximetil)-2,5-dihidro-2-furil]pirimidin-2(1*H*)-ona*antiviral*C₉H₁₀FN₃O₃

181785-84-2

**epitumomabum cituxetanum**

epitumomab cituxetan

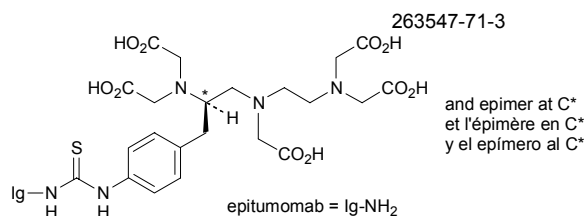
conjugate of 4-[(2*RS*)-2-[bis(carboxyméthyl)amino]-3-({2-[bis(carboxyméthyl)amino]éthyl}(carboxyméthyl)amino)propyl]phényl isothiocyanate forming a thiourea with the 6-amino of a lysine of immunoglobulin G1, anti-(human episialin) (mouse monoclonal HMFG-1 γ 1-chain), disulfide with mouse monoclonal HMFG-1 light chain, dimer*immunomodulator*

épitumomab cituxétan

dérivé de la thiourée produite par réaction de l'isothiocyanate de 4-[(2*RS*)-2-[bis(carboxyméthyl)amino]-3-[[2-[bis(carboxyméthyl)amino]éthyl](carboxyméthyl)amino]propyl]phényle avec le 6-amino d'une lysine de l'immunoglobuline G1, anti-(human episialin) ; dimère du disulfure entre la chaîne γ 1 et la chaîne légère de l'anticorps monoclonal de souris HMFG-1*immunomodulateur*

epitumomab cituxetán

derivado de la tiourea producido por reacción del isotiocianato de 4-[(2*RS*)-2-[bis(carboximetil)amino]-3-[[2-[bis(carboximetil)amino]etil](carboximetil)amino]propil]fenil con el 6-amino de una lisina de la inmunoglobulina G1, anti-(episialina humana) ; dímero del disulfuro entre la cadena γ 1 y la cadena ligera del anticuerpo monoclonal de ratón HMFG-1*immunomodulador*



eptoterminum alfa
eptotermín alfa

human recombinant bone morphogenetic protein 7 (hrBMP-7) or osteogenic protein-1 (OP-1)

growth factor

eptotermine alfa

protéine-7 humaine recombinante morphogénique de l'os (PMOrh-7) ou protéine-1 ostéogénique (PO-1)

facteur de croissance

eptotermína alfa

proteína-7 humana recombinante morfogénicas de hueso (PMOrh-7) o proteína-1 osteogénica (PO-1)

factor de crecimiento

[C₆₈₃H₁₀₆₁N₁₉₇O₂₀₈S₁₀]₂

129805-33-0

STGSKQRSQN	RSKTPKNQEA	LRMANVAENS	SSDQRQACKK
HELYVSFRDL	GWQDWIIAPE	GYAAYCEGE	CAFPLNSYMN
ATNHAIVQTL	VHFINPETVP	KPCCAPTQLN	AISVLYFDSS
SNVILKKYRN	MVVRACGCH		

exatecanum alideximerum
exatecan alideximer

exatecan linked via the tetrapeptide (glycylglycyl-L-phenylalanyl-glycyl) to poly[oxy(2-hydroxymethylethylene)=oxy(hydroxymethylmethylene)] partly O-substituted with carboxymethyl groups with some carboxy groups amide linked to the tetrapeptide.

antineoplastic

exatécán alideximer

exatécán lié par une chaîne tétrapeptidique (glycylglycyl-L-phénylalanyl-glycyl) à des éthers carboxyméthyliques de poly[oxy-(2-hydroxyéthylidène)oxy[1-(hydroxyméthyl)éthylène]]

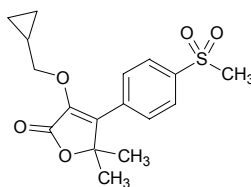
antineoplásique

exatecán alideximero

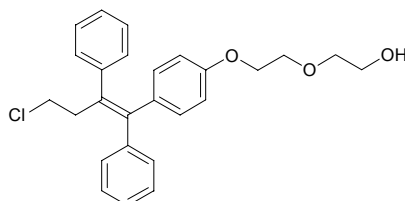
exatecán ligado por una cadena tetrapeptídica (glicilglicil-L-fenilalanilglicil) a éteres carboximetílicos de poli[oxy-(2-hidroxi-etilideno)oxi[1-(hidroximetil)etileno]]

antineoplásico

firocoxibum firocoxib	3-(cyclopropylmethoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]furan-2(5H)-one <i>cyclooxygenase-2 inhibitor</i>
firocoxib	3-(cyclopropylméthoxy)-5,5-diméthyl-4-[4-(méthylsulfonyl)phényl]furan-2(5H)-one <i>anti-inflammatoire</i>
firocoxib	3-(ciclopropilmetoxi)-5,5-dimetil-4-[4-(metilsulfonyl)fenil]furan-2(5H)-ona <i>inhibidor de la ciclooxigenasa-2</i>
	C ₁₇ H ₂₀ O ₅ S
	189954-96-9



fispemifenum fispemifene	2-(2-[4-[(1Z)-4-chloro-1,2-diphenylbut-1-enyl]phenoxy]ethoxy)ethanol <i>antiestrogen</i>
fispémifène	2-[2-[4-[(1Z)-4-chloro-1,2-diphénylbut-1-ényl]phénoxy]éthoxy]éthanol <i>anti-œstrogène</i>
fispemifeno	2-(2-[4-[(1Z)-4-cloro-1,2-difenilbut-1-enil]fenoxi]etoxi)etanol <i>antiestrógeno</i>
	C ₂₆ H ₂₇ ClO ₃
	341524-89-8



fluoresceinum liscolum

fluorescein lisicol

*N*⁶-({3',6'-dihydroxy-3-oxospiro[isobenzofuran-1(3H),9'-xanthen]-5-yl}thiocarbamoyl)-*N*²-(3 α ,7 α ,12 α -trihydroxy-5 β -cholan-24-oyl)-L-lysine

diagnostic aid

fluorescéine lisicol

acide (2*S*)-6-[[{(3',6'-dihydroxy-3-oxospiro[isobenzofurane-1(3*H*),9'-[9*H*]xanthén]-5-yl}thiocarbamoyl)amino]-2-[(3 α ,7 α ,12 α -trihydroxy-5 β -cholan-24-oyl)amino]pentanoïque

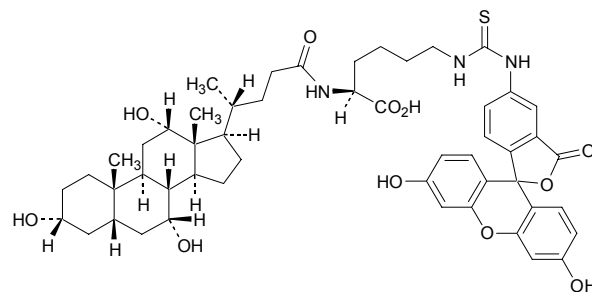
produit à usage diagnostique

fluoresceina lisicol

ácido 5-[[{(5*S*)-5-carboxi-5-[(3 α ,7 α ,12 α -trihidroxi-5 β -colan-24-oil)amino]pentil]tiocarbamoil)amino]-2-(6-hidroxi-3-oxo-3*H*-xanten-9-il)benzoico

*agente de diagnóstico*C₅₁H₆₃N₃O₁₁S

140616-46-2

**freselestatum**

freselestat

2-[5-amino-6-oxo-2-phenylpyrimidin-1(6*H*)-yl]-*N*-[(1*RS*)-1-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-3-methyl-1-oxobutan-2-yl]acetamide

elastase inhibitor

frésélestat

2-(5-amino-6-oxo-2-phénylpyrimidin-1(6*H*)-yl)-*N*-[(1*RS*)-1-[[5-(1,1-diméthyléthyl)-1,3,4-oxadiazol-2-yl]carbonyl]-2-méthylpropyl]=acétamide

inhibiteur de l'élastase

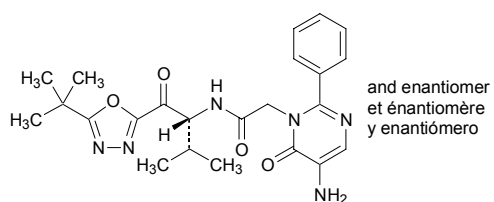
freselestat

2-[5-amino-6-oxo-2-fenilpirimidin-1(6*H*)-il]-*N*-[(1*RS*)-1-(5-*terc*-butil-1,3,4-oxadiazol-2-il)-3-metil-1-oxobutan-2-il]acetamida

inhibidor de la elastasa

$C_{23}H_{28}N_6O_4$

208848-19-5



galiximabum
galiximab

immunoglobulin G1, anti-(human CD80 (antigen)) (human-*Macaca irus* monoclonal IDEC-114 heavy chain), disulfide with human-*Macaca irus* monoclonal IDEC-114 λ chain, dimer

immunomodulator

galiximab

immunoglobuline G1, anti-(antigène CD80 humain), dimère du disulfure entre la chaîne λ et la chaîne lourde de l'anticorps monoclonal chimérique homme-macaque (*Macaca irus*) IDEC-114

immunomodulateur

galiximab

inmunoglobulina G1, anti-(antígeno CD80 humano), dímero del disulfuro entre la cadena λ y la cadena pesada del anticuerpo monoclonal quimérico hombre-macaco (*Macaca irus*) IDEC-114

inmunomodulador

357613-77-5

hemoglobinum raffimerum

hemoglobin raffimer

the polyaldehyde [(2*R*,4*S*,6*R*,8*R*,11*S*,13*R*)-1,14-dihydroxy-4-hydroxymethyl-3,5,7,10,12-pentaoxatetradecane-2,4,6,8,11,13-hexacarbaldéhyde] derived from raffinose [β -D-fructofuranosyl α -D-galactopyranosyl-(1 \rightarrow 6)- α -D-glucopyranoside] by treatment with sodium periodate is reacted with human hemoglobin A₀ at the 2,3-DPG binding pocket. Both intermolecular and intramolecular crosslinking occurs. This product is reduced to generate covalent amine bonds with >95% crosslinked hemoglobin of which about 55% is polymerised.

oxygen carrier

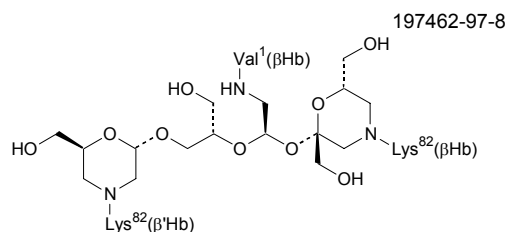
hémoglobine raffimer

hémoglobine stabilisée et partiellement polymérisée, obtenue par réduction du produit de la réaction du (2*R*,4*S*,6*R*,8*R*,11*S*,13*R*)-1,14-dihydroxy-4-(hydroxyméthyl)-3,5,7,10,12-pentaoxatétradécane-2,4,6,8,11,13-hexacarbaldéhyde (obtenu par oxydation périodique du raffinose) avec l'hémoglobine humaine

porteur d'oxygène

hemoglobina rafimero

hemoglobina estabilizada y parcialmente polimerizada, obtenida por reducción del producto de la reacción del (2*R*,4*S*,6*R*,8*R*,11*S*,13*R*)-1,14-dihidroxi-4-(hidroximetil)-3,5,7,10,12-pentaoxatetradecano-2,4,6,8,11,13-hexacarbaldéhidó (obtenido por oxidación periódica de la rafinosa) con la hemoglobina humana

transportador de oxígeno**icofungipenum**

icofungipen

(1*R*,2*S*)-2-amino-4-methylenecyclopentane-1-carboxylic acid*antifungal*

icofungipen

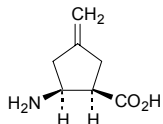
(-)-acide (1*R*,2*S*)-2-amino-4-méthylèncyclopentanecarboxylique*antifongique*

icofungipeno

(-)-ácido (1*R*,2*S*)-2-amino-4-metilenociclopentanocarboxílico*antifúngico*

C₇H₁₁NO₂

198022-65-0



icrocaptidum
icrocaptide

glycyl-*N*²-ethyl-L-lysyl-L-prolyl-L-arginine*anti-inflammatory*

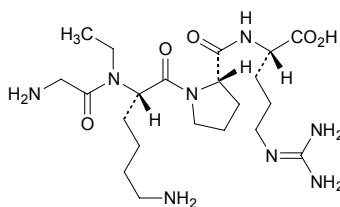
icrocaptide

glycyl-(*N*²-éthyl-L-lysyl)-L-prolyl-L-arginine*anti-inflammatoire*

icrocaptida

glicil-(*N*²-etil-L-lisil)-L-prolil-L-arginina*antiinflamatorio*C₂₁H₄₀N₈O₅

169543-49-1



iferanserinum
iferanserin

(E)-2'-[2-[(2S)-1-methyl-2-piperidyl]ethyl]cinnamamide

serotonin receptor antagonist

iféransérine

(-)-(2E)-N-[2-[2-[(2S)-1-méthylpipéridin-2-yl]éthyl]phényl]-3-phénylprop-2-énamide

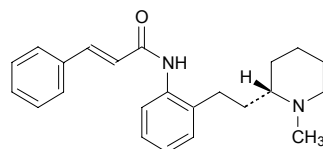
antagoniste de la sérotonine

iferanserina

(-)-(2E)-N-(2-[2-[(2S)-1-metilpiperidin-2-il]etil]fenil)-3-fenilprop-2-enamida

*antagonista de los receptores de la serotonina*C₂₃H₂₈N₂O

58754-46-4



istradefyllinum

istradefylline

8-[(*E*)-2-(3,4-dimethoxyphenyl)viny]-1,3-diethyl-7-methyl-3,7-dihydro-1*H*-purin-2,6-dione*antiparkinsonian*

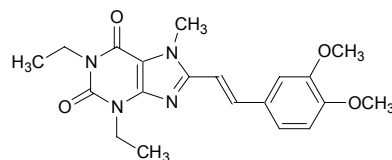
istradéfylline

8-[(*E*)-2-(3,4-diméthoxyphényl)éthényl]-1,3-diéthyl-7-méthyl-3,7-dihydro-1*H*-purin-2,6-dione*antiparkinsonien*

istradefilina

8-[(*E*)-2-(3,4-dimetoxifenil)vinil]-1,3-dietil-7-metil-3,7-dihidro-1*H*-purin-2,6-diona*antiparkinsoniano*C₂₀H₂₄N₄O₄

155270-99-8

**ixabepilonum**

ixabepilone

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1-(2-methyl-1,3-thiazol-4-yl)prop-1-en-2-yl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione*antineoplastic*

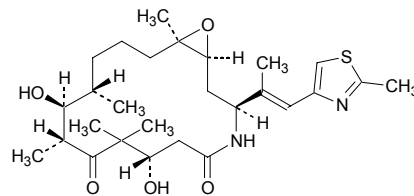
ixabépilone

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-dihydroxy-8,8,10,12,16-pentaméthyl-3-[(1*E*)-1-méthyl-2-(2-méthylthiazol-4-yl)éthényl]-17-oxa-4-azabicyclo[14.1.0]heptadécane-5,9-dione*antinéoplasique*

ixabepilona

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-dihidroxi-8,8,10,12,16-pentametil-3-[(1*E*)-1-(2-metil-1,3-tiazol-4-il)prop-1-en-2-il]-17-oxa-4-azabicyclo[14.1.0]heptadecano-5,9-diona*antineoplásico*C₂₇H₄₂N₂O₅S

219989-84-1



ladostigilum

ladostigil

(3*R*)-3-(prop-2-ynylamino)indan-5-yl ethyl(methyl)carbamate*cholinesterase and monoamine oxidase inhibitor*

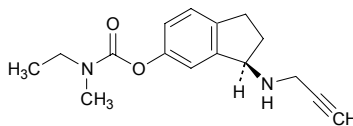
ladostigil

éthylméthylcarbamate de (3*R*)-3-(prop-2-ynylamino)-2,3-dihydro-1*H*-indén-5-yle*inhibiteur des acétylcholinestérasés et monoamines oxydases*

ladostigilo

etilmetilcarbamato de (3*R*)-3-(prop-2-inilamino)indan-5-ilo*inhibidor de acetilcolinesterasas y monoaminoxidasas*C₁₆H₂₀N₂O₂

209394-27-4

**lapatinibum**

lapatinib

N-[3-chloro-4-(3-fluorobenzoyloxy)phenyl]-6-[5-({[2-(methylsulfonyl)ethyl]amino)methyl]-2-furyl]quinazolin-4-amine

antineoplastic

lapatinib

N-[3-chloro-4-[(3-fluorobenzyl)oxy]phenyl]-6-[5-[[[2-(methylsulfonyl)ethyl]amino]methyl]-2-furyl]quinazolin-4-amine

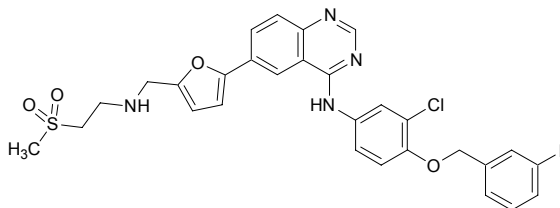
antineoplasique

lapatinib

N-[3-cloro-4-(3-fluorobenciloxi)fenil]-6-[5-({[2-(metilsulfonyl)etil]amino}metil)-2-furil]quinazolin-4-amina

*antineoplásico*C₂₉H₂₆ClFN₄O₄S

231277-92-2



lomeguatribum

lomeguatrib

6-(4-bromophenoxy)-7H-purin-2-amine

alkylguanine alkyltransferase inhibitor

lomeguatrib

6-[(4-bromothiophen-2-yl)methoxy]-7H-purin-2-amine

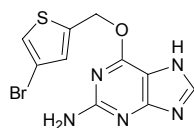
inhibiteur de l'alkyltransférase des alkylguanines

lomeguatrib

6-(4-bromoteniłoxi)-7H-purin-2-amina

*inhibidor de la alquiltransferasa de alquilguaninas*C₁₀H₈BrN₅OS

192441-08-0

**odiparcilum**

odiparcil

4-methyl-7-(5-thio-β-D-xylopyranosyloxy)-2H-chromen-2-one

antithrombotic

odiparcil

4-méthyl-7-[(5-thio-β-D-xylopyranosyl)oxy]-2H-1-benzopyran-2-one

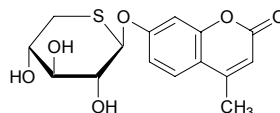
antithrombotique

odiparcilo

4-metil-7-(5-tio-β-D-xilopiranosiloxi)-2H-cromen-2-ona

*antitrombótico*C₁₅H₁₆O₆S

137215-12-4

**omigananum**

omiganan

L-isoleucyl-L-leucyl-L-arginyl-L-tryptophyl-L-prolyl-L-tryptophyl-L-tryptophyl-L-prolyl-L-tryptophyl-L-arginyl-L-arginyl-L-lysineamide

antimicrobial

omiganan

L-isoleucyl-L-leucyl-L-arginyl-L-tryptophyl-L-prolyl-L-tryptophyl-L-tryptophyl-L-prolyl-L-tryptophyl-L-arginyl-L-arginyl-L-lysineamide

antimicrobien

omiganán

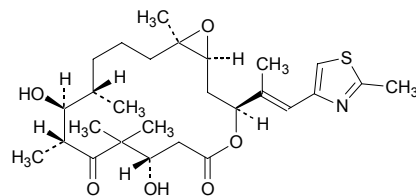
L-isoleucil-L-leucil-L-arginil-L-triptofil-L-prolil-L-triptofil-L-triptofil-L-prolil-L-triptofil-L-arginil-L-arginil-L-lisinamida

antimicrobiano

	$C_{90}H_{127}N_{27}O_{12}$	204248-78-2
	H-Ile-Leu-Arg-Trp-Pro-Trp-Trp-Pro-Trp-Arg-Arg-Lys-NH ₂ 10	
pactimibum pactimibe	[7-(2,2-dimethylpropanamido)-4,6-dimethyl-1-octylindolin-5-yl]acetic acid <i>antiatherosclerotic</i>	
pactimibe	acide [7-[(2,2-diméthylpropanoyl)amino]-4,6-diméthyl-1-octyl-2,3-dihydro-1 <i>H</i> -indol-5-yl]acétique <i>anti-athéromateux</i>	
pactimiba	ácido [7-(2,2-dimetilpropanamido)-4,6-dimetil-1-octilindolin-5-il]=acético <i>antiateromatoso</i>	
	$C_{25}H_{40}N_2O_3$	189198-30-9
patupilonum patupilone	(1 <i>S</i> ,3 <i>S</i> ,7 <i>S</i> ,10 <i>R</i> ,11 <i>S</i> ,12 <i>S</i> ,16 <i>R</i>)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[(1 <i>E</i>)-1-(2-methyl-1,3-thiazol-4-yl)prop-1-en-2-yl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione <i>antineoplastic</i>	
patupilone	(1 <i>S</i> ,3 <i>S</i> ,7 <i>S</i> ,10 <i>R</i> ,11 <i>S</i> ,12 <i>S</i> ,16 <i>R</i>)-7,11-dihydroxy-8,8,10,12,16-pentaméthyl-3-[(1 <i>E</i>)-1-méthyl-2-(2-méthylthiazol-4-yl)éthényl]-4,17-dioxabicyclo[14.1.0]heptadécane-5,9-dione <i>antinéoplasique</i>	
patupilona	(1 <i>S</i> ,3 <i>S</i> ,7 <i>S</i> ,10 <i>R</i> ,11 <i>S</i> ,12 <i>S</i> ,16 <i>R</i>)-7,11-dihidroxi-8,8,10,12,16-pentametil-3-[(1 <i>E</i>)-1-(2-metil-1,3-tiazol-4-il)prop-1-en-2-il]-4,17-dioxabicyclo[14.1.0]heptadecano-5,9-diona <i>antineoplásico</i>	

C₂₇H₄₁NO₆S

152044-54-7

**pertuzumabum**

pertuzumab

immunoglobulin G1, anti-(human v (receptor)) (human-mouse monoclonal 2C4 heavy chain), disulfide with human-mouse monoclonal 2C4 κ-chain, dimer

immunomodulator

pertuzumab

immunoglobuline G1, anti-(récepteur v humain), dimère du disulfure entre la chaîne κ et la chaîne lourde de l'anticorps monoclonal de souris humanisé 2C4

immunomodulateur

pertuzumab

immunoglobulina G1, anti-(receptor v humano), dímero del disulfuro entre la cadena κ y la cadena pesada del anticuerpo monoclonal humanizado de ratón 2C4

immunomodulador

380610-27-5

pixantronum

pixantrone

6,9-bis[(2-aminoethyl)amino]benzo[g]isoquinoline-5,10-dione

antineoplastic

pixantrone

6,9-bis[(2-aminoéthyl)amino]benzo[g]isoquinoléine-5,10-dione

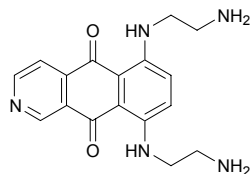
antinéoplasique

pixantrona

6,9-bis[(2-aminoetil)amino]benzo[g]isoquinolina-5,10-diona

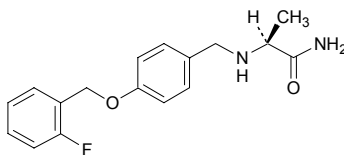
*antineoplásico*C₁₇H₁₉N₅O₂

144510-96-3



pritumumabum pritumumab	immunoglobulin G, anti-(human vimentin) (human monoclonal CLN G11 γ 1-chain), disulfide with human monoclonal CLN G11 κ -chain, dimer <i>antineoplastic</i>
pritumumab	immunoglobuline G, anti-(vimentine humaine) ; dimère du disulfure entre la chaîne γ 1 et la chaîne κ de l'anticorps monoclonal humain CLN H11 <i>antinéoplasique</i>
pritumumab	immunoglobulina G, anti-(vimentina humana); dímero del disulfuro entre la cadena γ 1 y la cadena κ del anticuerpo monoclonal humano CLN H11 <i>antineoplásico</i>
	$C_{6440}H_{9968}N_{1708}O_{2016}S_{42}$ 499212-74-7

ralfinamidum ralfinamide	(2S)-2-[4-(2-fluorobenzyloxy)benzylamino]propanamide <i>analgesic, sodium channel blocker</i>
ralfinamide	(+)-(2S)-2-[[4-[(2-fluorobenzyl)oxy]benzyl]amino]propanamide <i>analgésique, antagoniste des canaux sodiques</i>
ralfinamida	(+)-(2S)-2-[4-(2-fluorobenciloxi)encilamino]propanamide <i>analgésico, bloqueador de los canales del sodio</i>
	$C_{17}H_{19}FN_2O_2$ 133865-88-0



rebimastatum

rebimastat

N-[(2S)-2-sulfanyl-4-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)butanoyl]-L-leucyl-N¹,3-dimethyl-L-valinamide*matrix metalloproteinase inhibitor*

rébimastat

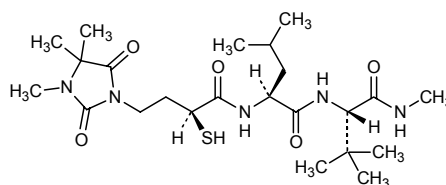
(2S)-N-[(1S)-2,2-diméthyl-1-(méthylcarbamoyl)propyl]-4-méthyl-2-[[[(2S)-2-sulfanyl-4-(3,4,4-triméthyl-2,5-dioxoimidazolidin-1-yl)butanoyl]amino]pentanamide

inhibiteur de la métalloprotéinase de la matrice

rebimastat

N-[(2S)-2-sulfanil-4-(3,4,4-trimetil-2,5-dioxoimidazolidin-1-il)butanoil]-L-leucil-N¹,3-dimetil-L-valinamida*inhibidor de la metaloproteinasas de matriz*C₂₃H₄₁N₅O₅S

259188-38-0

**segesteronum**

segesterone

17-hydroxy-16-methylene-19-norpregn-4-ene-3,20-dione

contraceptive

ségestérone

17-hydroxy-16-méthylène-19-norprégn-4-ène-3,20-dione

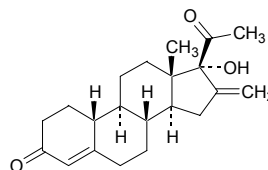
contraceptif

segesterona

17-hidroxi-16-metileno-19-norpregn-4-eno-3,20-diona

*contraceptivo*C₂₁H₂₈O₃

7690-08-6



semapimodum
semapimod*N,N'*-bis[3,5-bis[1-(carbamimidoylhydrazono)ethyl]phenyl]=
decanediamide*immunomodulator*

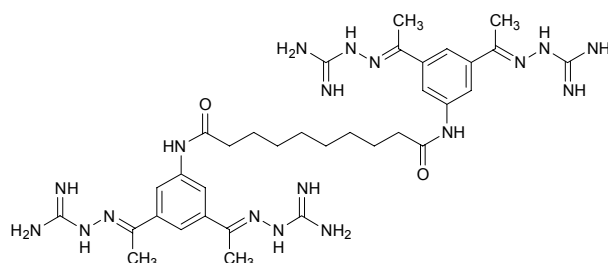
sémapimod

N,N'-bis[3,5-bis[*N*-(carbamimidoylamino)acétimidoyl]phényl]=
décanediamide*immunomodulateur*

semapimod

N,N'-bis[3,5-bis[1-(carbamimidoylhidrazono)etil]fenil]decanodiamida*inmunomodulador*C₃₄H₅₂N₁₈O₂

352513-83-8

**sufugolixum**
sufugolix5-[[benzyl(methyl)amino]methyl]-1-(2,6-difluorobenzyl)-6-[4-(3-methoxyureido)phenyl]-3-phenylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione*luteinizing hormone-releasing-hormone (LHRH) antagonist*

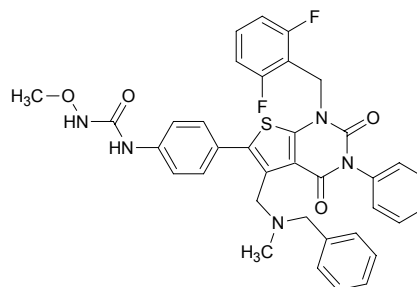
sufugolix

1-[4-[5-[(benzylméthylamino)méthyl]-1-(2,6-difluorobenzyl)-2,4-dioxo-3-phényl-1,2,3,4-tétrahydrothiéno[2,3-*d*]pyrimidin-6-yl]phényl]-3-méthoxyurée*antagoniste de l'hormone de liberation de la lutéostimuline*

sufugolix

5-[[bencil(metil)amino]metil]-1-(2,6-difluorobencil)-6-[4-(3-metoxiureido)fenil]-3-feniltieno[2,3-*d*]pirimidina-2,4(1*H*,3*H*)-diona*antagonista de la hormona de liberación de hormona luteinizante*C₃₆H₃₁F₂N₅O₄S

308831-61-0



tafluprostum

tafluprost

isopropyl (5Z)-7-[(1R,2R,3R,5S)-2-[(1E)-3,3-difluoro-4-phenoxybut-1-enyl]-3,5-dihydroxycyclopentyl]hept-5-enoate

antiglaucoma

tafluprost

(5Z)-7-[(1R,2R,3R,5S)-2-[(1E)-3,3-difluoro-4-phénoxybut-1-ényl]-3,5-dihydroxycyclopentyl]hept-5-énoate de 1-méthyléthyle

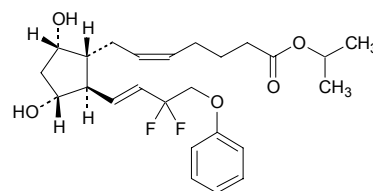
antiglaucmateux

tafluprost

(5Z)-7-[(1R,2R,3R,5S)-2-[(1E)-3,3-difluoro-4-fenoxibut-1-enil]-3,5-dihidroxiciclopentil]hept-5-enoato de isopropilo

*antiglaucoma*C₂₅H₃₄F₂O₅

209860-87-7

**talizumabum**

talizumab

immunoglobulin G, anti-(human immunoglobulin E Fc region) (human-mouse monoclonal Hu901 γ -chain), disulfide with human-mouse monoclonal Hu901 κ -chain, dimer*immunomodulator*

talizumab

immunoglobuline G, anti-(région Fc de l'immunoglobuline E humaine), dimère du disulfure entre la chaîne κ et la chaîne γ de l'anticorps monoclonal de souris humanisé Hu901*immunomodulateur*

talizumab

immunoglobulina G, anti-(región Fc de la inmunoglobulina E humana), dímero del disulfuro entre la cadena κ y la cadena γ del anticuerpo monoclonal humanizado de ratón Hu901*inmunomodulador*

380610-22-0

technetium (99mTc) nitridocadum

technetium (99mTc) nitridocade

(SPY-5-21)-bis[ethoxy(ethyl)dithiocarbamato-κS,κS']=
nitrido[^{99m}Tc]technetium*radiodiagnostic agent*

technétium (99mTc) nitridocade

(SPY-5-21)-bis(éthoxyéthyl)dithiocarbamato-κS,κS')=
nitrido[^{99m}Tc]technétium*produit à usage radiodiagnostique*

tecnecio (99mTc) nitridocado

(SPY-5-21)-bis(etoxietilditiocarbamato-κS,κS')nitrido[^{99m}Tc]tecnecio*agente de radiodiagnóstico*C₁₀H₂₀N₃O₂S₄^{99m}Tc

131608-78-1

**tesofensinum**

tesofensine

(1R,2R,3S,5S)-3-(3,4-dichlorophenyl)-2-(ethoxymethyl)-8-methyl-8-
azabicyclo[3.2.1]octane*antiparkinsonian*

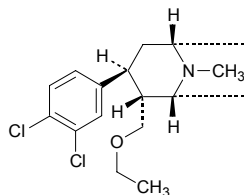
tésofensine

(1R,2R,3S,5S)-3-(3,4-dichlorophényl)-2-(éthoxyméthyl)-8-méthyl-8-
azabicyclo[3.2.1]octane*antiparkinsonien*

tesofensina

(1R,2R,3S,5S)-3-(3,4-diclorofenil)-2-(etoximetil)-8-metil-8-
azabicyclo[3.2.1]octano*antiparkinsoniano*C₁₇H₂₃Cl₂NO

195875-84-4



tifenazoxidum

tifenazoxide

6-chloro-*N*-(1-methylcyclopropyl)-1,1-dioxo-1,4-dihydro-1λ⁶-thieno[3,2-*e*][1,2,4]thiadiazin-3-amine*antidiabetic*

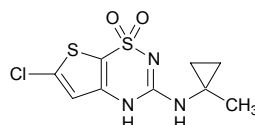
tifénazoxide

1,1-dioxyde de 6-chloro-*N*-(1-méthylcyclopropyl)-4*H*-thiéno[3,2-*e*]-1,2,4-thiadiazin-3-amine*antidiabétique*

tifenazóxido

1,1-dióxido de 6-cloro-*N*-(1-metilciclopropil)-4*H*-tieno[3,2-*e*]-1,2,4-tiadiazin-3-amina*antidiabético*C₉H₁₀ClN₃O₂S₂

279215-43-9

**tisocalcitatum**

tisocalcitate

isopropyl (1*S*,3*R*,5*Z*,7*E*,22*E*,24*R*)-1,3,24-trihydroxy-9,10-secocholesta-5,7,10(19),22-tetraene-25-carboxylate*vitamin D analogue*

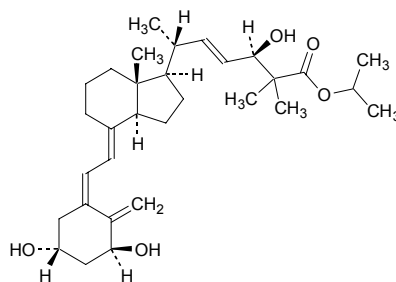
tisocalcitate

(5*Z*,7*E*,22*E*,24*R*)-1α,3β,24-trihydroxy-9,10-sécocholesta-5,7,10(19),22-tétraène-25-carboxylate de 1-méthyléthyle*analogue de la vitamine D*

tisocalcitato

(1*S*,3*R*,5*Z*,7*E*,22*E*,24*R*)-1,3,24-trihidroxi-9,10-secocolesta-5,7,10(19),22-tetraeno-25-carboxilato de isopropilo*análogo de la vitamina D*C₃₁H₄₈O₅

156965-06-9



ulifloxacinum

ulifloxacin

(1*RS*)-6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid*antibacterial*

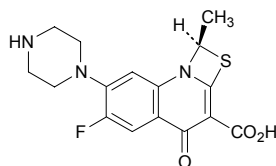
ulifloxacin

acide (1*RS*)-6-fluoro-1-méthyl-4-oxo-7-(pipérazin-1-yl)-4*H*-[1,3]thiazéto[3,2-*a*]quinoléine-3-carboxylique*antibactérien*

ulifloxacin

ácido (1*RS*)-6-fluoro-1-metil-4-oxo-7-(piperazin-1-il)-4*H*-[1,3]tiazeto[3,2-*a*]quinolina-3-carboxílico*antibacteriano*C₁₆H₁₆FN₃O₃S

112984-60-8

and enantiomer
et énantiomère
y enantiómero**vareniclinum**

varenicline

7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxaline*nicotinic acetylcholine receptor agonist*

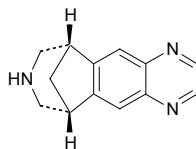
varénicline

(6*R*,10*S*)-7,8,9,10-tétrahydro-6,10-méthano-6*H*-pyrazino[2,3-*h*][3]benzazépine*agoniste des récepteurs nicotiques à l'acétylcholine*

vareniclina

7,8,9,10-tetrahydro-6*H*-6,10-metanoazepino[4,5-*g*]quinoxalina*agonista de los receptores nicotínicos de la acetilcolina*C₁₃H₁₃N₃

249296-44-4



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

**Proposed International Nonproprietary Names (Prop. INN): List 87
Dénominations communes internationales proposées (DCI Prop.): Liste 87
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 87
(WHO Drug Information, Vol. 16, No. 2, 2002)**

- p. 160 **asenapinum**
 asenapine
 asénapine
 asenapina
*replace the CAS registry number by the following:
 remplacer le numéro dans le registre du CAS par :
 sustitúyase el número de registro del CAS por:*
 65576-45-6
- p. 161 **axomadolum**
 axomadol
 axomadol
 axomadol
*replace the molecular formula by the following:
 remplacer la formule brute par :
 sustitúyase la fórmula molecular por:*
 $C_{16}H_{25}NO_3$
- p. 166 **elzasonanum**
 elzasonan
 elzasonan
 elzasonán
*add the following CAS registry number:
 insérer le numéro dans le registre du CAS suivant :
 insértese el número de registro del CAS siguiente:*
 361343-19-3
- p. 167 **enecadinum**
 enecadin
 énécadine
 enecadina
*add the following CAS registry number:
 insérer le numéro dans le registre du CAS suivant :
 insértese el número de registro del CAS siguiente:*
 259525-01-4
- p. 170 **idusulfasum**
 idusulfase
 idusulfase
 idusulfasa
*replace the molecular formula by the following:
 remplacer la formule brute par :
 sustitúyase la fórmula molecular por:*
 $C_{2688}H_{4057}N_{699}O_{792}S_{14}$
- p. 173 **lubiprostonum**
 lubiprostone
 lubiprostone
 lubiprostona
*replace the CAS registry number by the following:
 remplacer le numéro dans le registre du CAS par :
 sustitúyase el número de registro del CAS por:*
 333963-40-9
- p. 182 **plevitrexedum**
 plevitrexed
 plévitrexed
 plevitrexed
*replace the molecular formula by the following:
 remplacer la formule brute par :
 sustitúyase la fórmula molecular por:*
 $C_{26}H_{25}FN_8O_4$

p. 184 **tapentadolum**

tapentadol
tapentadol
tapentadol

*replace the CAS registry number by the following:
remplacer le numéro dans le registre du CAS par :
sustitúyase el número de registro del CAS por:*

175591-23-8

Proposed International Nonproprietary Names (Prop. INN): List 88
Dénominations communes internationales proposées (DCI Prop.): Liste 88
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 88
(WHO Drug Information, Vol. 17, No. 1, 2003)

p. 46 **asoprisnili ecamas**

asoprisnil ecamate
écamate d'asoprisnil
ecamato de asoprisnil

*replace the CAS registry number by the following:
remplacer le numéro dans le registre du CAS par :
sustitúyase el número de registro del CAS por:*

222732-94-7

Annex 1

PROCEDURE FOR THE SELECTION OF RECOMMENDED INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES*

The following procedure shall be followed by the World Health Organization in the selection of recommended international nonproprietary names for pharmaceutical substances, in accordance with the World Health Assembly resolution WHA3.11:

1. Proposals for recommended international nonproprietary names shall be submitted to the World Health Organization on the form provided therefor.

2. Such proposals shall be submitted by the Director-General of the World Health Organization to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated for this purpose, for consideration in accordance with the "General principles for guidance in devising International Nonproprietary Names", appended to this procedure. The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

3. Subsequent to the examination provided for in article 2, the Director-General of the World Health Organization shall give notice that a proposed international nonproprietary name is being considered.

A. Such notice shall be given by publication in the *Chronicle of the World Health Organization*¹ and by letter to Member States and to national pharmacopoeia commissions or other bodies designated by Member States.

(i) Notice may also be sent to specific persons known to be concerned with a name under consideration.

B. Such notice shall:

(i) set forth the name under consideration;

(ii) identify the person who submitted a proposal for naming the substance, if so requested by such person;

(iii) identify the substance for which a name is being considered;

(iv) set forth the time within which comments and objections will be received and the person and place to whom they should be directed;

(v) state the authority under which the World Health Organization is acting and refer to these rules of procedure.

C. In forwarding the notice, the Director-General of the World Health Organization shall request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the proposed name during the period it is under consideration by the World Health Organization.

4. Comments on the proposed name may be forwarded by any person to the World Health Organization within four months of the date of publication, under article 3, of the name in the *Chronicle of the World Health Organization*.¹

5. A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in the *Chronicle of the World Health Organization*.¹

A. Such objection shall:

(i) identify the person objecting;

* Text adopted by the Executive Board of WHO in resolution EB15.R7 (*Off. Rec. Wld Health Org.*, 1955, 60, 3) and amended by the Board in resolution EB43.R9 (*Off. Rec. Wld Hlth Org.*, 1969, 173, 10).

¹ The title of this publication was changed to *WHO Chronicle* in January 1959. From 1987 onwards lists of INNs are published in *WHO Drug Information*.

(ii) state his interest in the name;

(iii) set forth the reasons for his objection to the name proposed.

6. Where there is a formal objection under article 5, the World Health Organization may either reconsider the proposed name or use its good offices to attempt to obtain withdrawal of the objection. Without prejudice to the consideration by the World Health Organization of a substitute name or names, a name shall not be selected by the World Health Organization as a recommended international nonproprietary name while there exists a formal objection thereto filed under article 5 which has not been withdrawn.

7. Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Director-General of the World Health Organization shall give notice in accordance with subsection A of article 3 that the name has been selected by the World Health Organization as a recommended international nonproprietary name.

8. In forwarding a recommended international nonproprietary name to Member States under article 7, the Director-General of the World Health Organization shall:

A. request that it be recognized as the nonproprietary name for the substance; and

B. request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name, including prohibiting registration of the name as a trade-mark or trade-name.

Annex 2

GENERAL PRINCIPLES FOR GUIDANCE IN DEVISING INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES*

1. International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names in common use.

2. The INN for a substance belonging to a group of pharmacologically related substances should, where appropriate, show this relationship. Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion should be avoided.

These primary principles are to be implemented by using the following secondary principles:

3. In devising the INN of the first substance in a new pharmacological group, consideration should be given to the possibility of devising suitable INN for related substances, belonging to the new group.

4. In devising INN for acids, one-word names are preferred; their salts should be named without modifying the acid name, e.g. "oxacillin" and "oxacillin sodium", "ibufenac" and "ibufenac sodium".

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ only in respect of the name of the inactive acid or the inactive base.

For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

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

* In its twentieth report (WHO Technical Report Series, No. 581, 1975), the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, international nonproprietary names (INN) in the light of developments in pharmaceutical compounds in recent years. The most significant change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves employing a characteristic "stem" indicative of a common property of the members of a group. The reasons for, and the implications of, the change are fully discussed.

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

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

9. Group relationship in INN (see Guiding Principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use.¹ Where a stem is shown without any hyphens it may be used anywhere in the name.

<i>Latin</i>	<i>English</i>	
-acum	-ac	anti-inflammatory agents of the ibufenac group
-actidium	-actide	synthetic polypeptides with a corticotropin-like action
-adolum	-adol)	analgetics
-adol-	-adol-)	
-astum	-ast	antiasthmatic, antiallergic substances not acting primarily as antihistaminics
-astinum	-astine	antihistaminics
-azepamum	-azepam	diazepam derivatives
-bactamum	-bactam	β-lactamase inhibitors
bol	bol	steroids, anabolic
-buzonium	-buzone	anti-inflammatory analgesics, phenylbutazone derivatives
-cain-	-cain-	antifibrilliant substances with local anaesthetic activity
-cainum	-caine	local anaesthetics
cef-	cef-	antibiotics, cephalosporanic acid derivatives
-cillinum	-cillin	antibiotics, derivatives of 6-aminopenicillanic acid
-conazolom	-conazole	systemic antifungal agents, miconazole derivatives
cort	cort	corticosteroids, except prednisolone derivatives
-dipinum	-dipine	calcium channel blockers, nifedipine derivatives
-fibratum	-fibrate	clofibrate derivatives
gest	gest	steroids, progestogens
gli-	gli-	sulfonamide hypoglycaemics
io-	io-	iodine-containing contrast media
-ium	-ium	quaternary ammonium compounds
-metacinum	-metacin	anti-inflammatory substances, indometacin derivatives
-mycinum	-mycin	antibiotics, produced by <i>Streptomyces</i> strains
-nidazolom	-nidazole	antiprotozoal substances, metronidazole derivatives
-ololum	-olol	β-adrenoreceptor antagonists
-oxacinum	-oxacin	antibacterial agents, nalidixic acid derivatives
-pidum	-pide	sulpiride derivatives
-pril(at)um	pril(at)	angiotensin-converting enzyme inhibitors
-profenum	-profen	anti-inflammatory substances, ibuprofen derivatives
prost	prost	prostaglandins
-relinum	-relin	hypophyseal hormone release-stimulating peptides
-terolum	-terol	bronchodilators, phenethylamine derivatives
-tidinum	-tidine	histamine H ₂ -receptor antagonists
-trexatum	-trexate	folic acid antagonists
-verinum	-verine	spasmolytics with a papaverine-like action
vin-	vin-)	vinca alkaloids
-vin-	-vin-)	

¹ A more extensive listing of stems is contained in the working document WHO/EDM/QSM 99.6 which is regularly updated and can be requested from the INN Programme, WHO, Geneva.

Annexe 1

PROCEDURE A SUIVRE EN VUE DU CHOIX DE DENOMINATIONS COMMUNES INTERNATIONALES RECOMMANDEES POUR LES SUBSTANCES PHARMACEUTIQUES*

L'Organisation mondiale de la Santé observe la procédure exposée ci-dessous pour l'attribution de dénominations communes internationales recommandées pour les substances pharmaceutiques, conformément à la résolution WHA3.11 de l'Assemblée mondiale de la Santé:

1. Les propositions de dénominations communes internationales recommandées sont soumises à l'Organisation mondiale de la Santé sur la formule prévue à cet effet.

2. Ces propositions sont soumises par le Directeur général de l'Organisation mondiale de la Santé aux experts désignés à cette fin parmi les personnalités inscrites au Tableau d'experts de la Pharmacopée internationale et des Préparations pharmaceutiques; elles sont examinées par les experts conformément aux "Directives générales pour la formation des dénominations communes internationales", reproduites ci-après. La dénomination acceptée est la dénomination employée par la personne qui découvre ou qui, la première, fabrique et lance sur le marché une substance pharmaceutique, à moins que des raisons majeures n'obligent à s'écarter de cette règle.

3. Après l'examen prévu à l'article 2, le Directeur général de l'Organisation mondiale de la Santé notifie qu'un projet de dénomination commune internationale est à l'étude.

A. Cette notification est faite par une insertion dans la *Chronique de l'Organisation mondiale de la Santé*¹ et par l'envoi d'une lettre aux Etats Membres et aux commissions nationales de pharmacopée ou autres organismes désignés par les Etats Membres.

(i) Notification peut également être faite à toute personne portant à la dénomination mise à l'étude un intérêt notoire.

B. Cette notification contient les indications suivantes:

(i) dénomination mise à l'étude;

(ii) nom de l'auteur de la proposition tendant à attribuer une dénomination à la substance, si cette personne le demande;

(iii) définition de la substance dont la dénomination est mise à l'étude;

(iv) délai pendant lequel seront reçues les observations et les objections à l'égard de cette dénomination; nom et adresse de la personne habilitée à recevoir ces observations et objections;

(v) mention des pouvoirs en vertu desquels agit l'Organisation mondiale de la Santé et référence au présent règlement.

C. En envoyant cette notification, le Directeur général de l'Organisation mondiale de la Santé demande aux Etats Membres de prendre les mesures nécessaires pour prévenir l'acquisition de droits de propriété sur la dénomination proposée pendant la période au cours de laquelle cette dénomination est mise à l'étude par l'Organisation mondiale de la Santé.

4. Des observations sur la dénomination proposée peuvent être adressées à l'Organisation mondiale de la Santé par toute personne, dans les quatre mois qui suivent la date de publication de la dénomination dans la *Chronique de l'Organisation mondiale de la Santé*¹ (voir l'article 3).

* Le texte reproduit ici a été adopté par le Conseil exécutif dans la résolution EB15.R7 (*Actes off. Org. mond. Santé*, 1955, 60, 3) qui l'a ultérieurement amendé par la résolution EB43.R9 (*Actes off. Org. mond. Santé*, 1969, 173, 10).

¹ Depuis janvier 1959, cette publication porte le titre de *Chronique OMS*. A partir de 1987, les listes des DCIs sont publiées dans les *Informations pharmaceutiques OMS*.

5. Toute personne intéressée peut formuler une objection formelle contre la dénomination proposée dans les quatre mois qui suivent la date de publication de la dénomination dans la *Chronique de l'Organisation mondiale de la Santé*¹ (voir l'article 3).

A. Cette objection doit s'accompagner des indications suivantes:

- i) nom de l'auteur de l'objection;
- ii) intérêt qu'il porte à la dénomination en cause;
- iii) raisons motivant l'objection contre la dénomination proposée.

6. Lorsqu'une objection formelle est formulée en vertu de l'article 5, l'Organisation mondiale de la Santé peut soit soumettre la dénomination proposée à un nouvel examen, soit intervenir pour tenter d'obtenir le retrait de l'objection. Sans préjudice de l'examen par elle d'une ou de plusieurs appellations de remplacement, l'Organisation mondiale de la Santé n'adopte pas d'appellation comme dénomination commune internationale recommandée tant qu'une objection formelle présentée conformément à l'article 5 n'est pas levée.

7. Lorsqu'il n'est formulé aucune objection en vertu de l'article 5 ou que toutes les objections présentées ont été levées, le Directeur général de l'Organisation mondiale de la Santé fait une notification conformément aux dispositions de la sous-section A de l'article 3, en indiquant que la dénomination a été choisie par l'Organisation mondiale de la Santé en tant que dénomination commune internationale recommandée.

8. En communiquant aux Etats Membres, conformément à l'article 7, une dénomination commune internationale recommandée, le Directeur général de l'Organisation mondiale de la Santé:

A. demande que cette dénomination soit reconnue comme dénomination commune de la substance considérée, et

B. demande aux Etats Membres de prendre les mesures nécessaires pour prévenir l'acquisition de droits de propriété sur cette dénomination, notamment en interdisant le dépôt de cette dénomination comme marque ou appellation commerciale.

Annexe 2

DIRECTIVES GENERALES POUR LA FORMATION DE DENOMINATIONS COMMUNES INTERNATIONALES APPLICABLES AUX SUBSTANCES PHARMACEUTIQUES*

1. Les dénominations communes internationales (DCI) devront se distinguer les unes des autres par leur consonance et leur orthographe. Elles ne devront pas être d'une longueur excessive, ni prêter à confusion avec des appellations déjà couramment employées.

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

Outre ces deux principes fondamentaux, on respectera les principes secondaires suivants:

* Dans son vingtième rapport (Série de Rapports techniques de l'OMS, No. 581, 1975), le Comité OMS d'experts des Dénominations communes pour les Substances pharmaceutiques a examiné les directives générales pour la formation des dénominations communes internationales et la procédure à suivre en vue de leur choix, compte tenu de l'évolution du secteur pharmaceutique au cours des dernières années. La modification la plus importante a été l'extension aux substances de synthèse de la pratique normalement suivie pour désigner les substances tirées ou dérivées de produits naturels. Cette pratique consiste à employer des syllabes communes ou groupes de syllabes communes (segments clés) qui sont caractéristiques et indiquent une propriété commune aux membres du groupe des substances pour lequel ces segments clés ont été retenus. Les raisons et les conséquences de cette modification ont fait l'objet de discussions approfondies.

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

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

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

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

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

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

8. On retiendra de préférence, pour autant qu'elles respectent les principes énoncés ici, les dénominations proposées par les personnes qui ont découvert ou qui, les premières, ont fabriqué et lancé sur le marché les préparations pharmaceutiques considérées, ou les dénominations déjà officiellement adoptées par un pays.

9. La parenté entre substances d'un même groupe (voir Directive générale 2) sera si possible indiquée dans les DCI par l'emploi de segments clés communs. La liste ci-après contient des exemples de segments clés pour des groupes de substances, surtout pour des groupes récents. Il y a beaucoup d'autres segments clés en utilisation active.¹ Les segments clés indiqués sans trait d'union pourront être insérés n'importe où dans une dénomination.

<i>Latin</i>	<i>Français</i>	
-acum	-ac	substances anti-inflammatoires du groupe de l'ibufénac
-actidum	-actide	polypeptides synthétiques agissant comme la corticotropine
-adolum	-adol) analgésiques
-adol-	-adol-)
-astum	-ast	antiasthmatiques, antiallergiques n'agissant pas principalement en tant
-astinum	-astine	antihistaminiques
-azepamum	-azépam	substances du groupe du diazépam
-bactamum	-bactame	inhibiteurs de β -lactamases
bol	bol	stéroïdes anabolisants
-buzonum	-buzone	analgésiques anti-inflammatoires du groupe de la phénylbutazone
-cain-	-caïn-	substances antifibrillantes à action anesthésique locale
-cainum	-caïne	anesthésiques locaux
cef-	céf-	antibiotiques, dérivés de l'acide céphalosporanique
-cillinum	-cilline	antibiotiques, dérivés de l'acide 6-aminopénicillanique
-conazolium	-conazole	agents antifongiques systémiques du groupe du miconazole
cort	cort	corticostéroïdes, autres que les dérivés de la prednisolone
-dipinum	-dipine	inhibiteurs du calcium du groupe de la nifédipine
-fibratum	-fibrate	substances du groupe du clofibrate
gest	gest	stéroïdes progestogènes
gli-	gli-	sulfamides hypoglycémiant
io-	io-	produits de contraste iodés
-ium	-ium	ammoniums quaternaires
-metacinum	-métacine	substances anti-inflammatoires du groupe de l'indométacine

¹ Une liste plus complète de segments clés est contenue dans le document de travail WHO/EDM/QSM 99.6 qui est régulièrement mis à jour et qui peut être demandé auprès du Programme des DCI, OMS, Genève.

Latin *Français*

-mycinum	-mycine	antibióticos producidos por cepas de <i>Streptomyces</i>
-nidazololum	-nidazole	substancias antiprotozoarias del grupo del metronidazol
ololum	-olol	antagonistas de los receptores β -adrenérgicos
-oxacinum	-oxacine	substancias antibacterianas del grupo del ácido nalidixico
-pridum	-pride	substancias del grupo del sulfpirido
-profenum	-profène	substancias anti-inflamatorias del grupo del ibuprofeno
-pril(at)um	-pril(ate)	inhibidores de la enzima de conversión de la angiotensina
prost	prost	prostaglandinas
-relinum	-réline	peptidos que estimulan la liberación de hormonas hipofisarias
-terolum	-térol	broncodilatadores, derivados de la fenétilamina
-tidinum	-tidine	antagonistas de los receptores H_2 de la histamina
-trexatum	-trexate	antagonistas del ácido fólico
-verinum	-vérine	espasmolíticos que actúan como la papaverina
vin-	vin-	alcaloides del tipo vinca
-vin-	-vin-)

Anexo 1

PROCEDIMIENTO DE SELECCION DE DENOMINACIONES COMUNES INTERNACIONALES RECOMENDADAS PARA LAS SUSTANCIAS FARMACEUTICAS*

La Organización Mundial de la Salud seguirá el procedimiento que se expone a continuación para la selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas, de conformidad con lo dispuesto en la resolución WHA3.11 de la Asamblea Mundial de la Salud:

1. Las propuestas de denominaciones comunes internacionales recomendadas se presentarán a la Organización Mundial de la Salud en los formularios que se proporcionen a estos efectos.
2. Estas propuestas serán sometidas por el Director General de la Organización Mundial de la Salud a los Miembros del Cuadro de Expertos de la Farmacopea Internacional y las Preparaciones Farmacéuticas encargados de su estudio, para que las examinen de conformidad con los "Principios Generales de Orientación para formar Denominaciones Comunes Internacionales para Sustancias Farmacéuticas", anexos a este Procedimiento. A menos que haya poderosas razones en contra, la denominación aceptada será la empleada por la persona que haya descubierto, fabricado o puesto a la venta por primera vez una sustancia farmacéutica.
3. Una vez terminado el estudio a que se refiere el artículo 2, el Director General de la Organización Mundial de la Salud notificará que está en estudio un proyecto de denominación internacional.
 - A. Esta notificación se hará mediante una publicación en la *Crónica de la Organización Mundial de la Salud*¹ y el envío de una carta a los Estados Miembros y a las comisiones nacionales de las farmacopeas u otros organismos designados por los Estados Miembros.
 - (i) La notificación puede enviarse también a las personas que tengan un interés especial en una denominación objeto de estudio.

* El texto corregido que aquí se reproduce fue adoptado por el Consejo Ejecutivo en la resolución EB15.R7 (*Act. of. Org. mund. Salud*, 1955, 60, 3) y enmendado por el Consejo en la resolución EB43.R9 (*Act. of. Org. mund. Salud*, 1969, 173, 10).

¹ Denominada *Crónica de la OMS* desde enero de 1959. A partir de 1987, las listas de DCI se publican en *Información Farmacéutica OMS*.

- B. En estas notificaciones se incluyen los siguientes datos:

-
- (i) denominación sometida a estudio;
 - (ii) nombre de la persona que ha presentado la propuesta de denominación de la sustancia si lo pide esta persona;
 - (iii) definición de la sustancia cuya denominación está en estudio;
 - (iv) plazo fijado para recibir observaciones y objeciones, así como nombre y dirección de la persona a quien deban dirigirse, y
 - (v) mención de los poderes conferidos para el caso a la Organización Mundial de la Salud y referencia al presente procedimiento.

C. Al enviar esta notificación, el Director General de la Organización Mundial de la Salud solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de propiedad sobre la denominación propuesta, durante el periodo en que la Organización Mundial de la Salud tenga en estudio esta denominación.

4. Toda persona puede formular a la Organización Mundial de la Salud observaciones sobre la denominación propuesta, dentro de los cuatro meses siguientes a su publicación en la *Crónica de la Organización Mundial de la Salud*, conforme a lo dispuesto en el artículo 3.

5. Toda persona interesada puede presentar una objeción formal contra la denominación propuesta, dentro de los cuatro meses siguientes a su publicación en la *Crónica de la Organización Mundial de la Salud*, conforme a lo dispuesto en el artículo 3.

A. Esta objeción deberá acompañarse de los siguientes datos:

- i) nombre de la persona que formula la objeción;
- ii) causas que motivan su interés por la denominación, y
- iii) causas que motivan su objeción a la denominación propuesta.

6. Cuando se haya presentado una objeción formal en la forma prevista en el artículo 5, la Organización Mundial de la Salud puede someter a nuevo estudio la denominación propuesta, o bien utilizar sus buenos oficios para lograr que se retire la objeción. Sin perjuicio de que la Organización Mundial de la Salud estudie una o varias denominaciones en sustitución de la primitiva, ninguna denominación podrá ser seleccionada por la Organización Mundial de la Salud como denominación común internacional recomendada en tanto que exista una objeción formal, presentada como previene el artículo 5, que no haya sido retirada.

7. Cuando no se haya formulado ninguna objeción en la forma prevista en el artículo 5, o cuando todas las objeciones presentadas hayan sido retiradas, el Director de la Organización Mundial de la Salud notificará, conforme a lo dispuesto en el párrafo A del artículo 3, que la denominación ha sido seleccionada por la Organización Mundial de la Salud como denominación común internacional recomendada.

8. Al comunicar a los Estados Miembros una denominación común internacional conforme a lo previsto en el artículo 7, el Director General de la Organización Mundial de la Salud:

- A. solicitará que esta denominación sea reconocida como denominación común para la sustancia de que se trate, y
- B. solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de propiedad sobre la denominación, incluso la prohibición de registrarla como marca de fábrica o como nombre comercial.

Anexo 2

PRINCIPIOS GENERALES DE ORIENTACION PARA FORMAR DENOMINACIONES COMUNES INTERNACIONALES PARA SUSTANCIAS FARMACEUTICAS*

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

2. La DCI de una sustancia que pertenezca a un grupo de sustancias farmacológicamente emparentadas deberá mostrar apropiadamente este parentesco. Deberán evitarse los nombres que puedan inducir fácilmente en el paciente sugerencias anatómicas, fisiológicas, patológicas o terapéuticas.

Estos principios primarios deberán ser tenidos en cuenta al aplicar los siguientes principios secundarios:

3. Al idear la DCI de la primera sustancia de un nuevo grupo farmacológico, deberá tenerse en cuenta la posibilidad de formar DCI convenientes para las sustancias emparentadas que vengan a incrementar el nuevo grupo.

4. Al idear DCI para ácidos, se preferirán las de una sola palabra; sus sales deberán denominarse sin modificar el nombre de ácido; p. ej., "oxacilina" y "oxacilina sódica", "ibufenaco" e "ibufenaco sódico".

5. Las DCI para las sustancias que se usan en forma de sal, deberán en general aplicarse a la base activa o, respectivamente, al ácido activo. Las denominaciones para diferentes sales o ésteres de la misma sustancia activa solamente deberán diferir en el nombre de ácido o de la base inactivos.

En los compuestos de amonio cuaternario, el catión y el anión deberán denominarse adecuadamente por separado, como componentes independientes de una sustancia cuaternaria y no como sales de una amina.

6. Deberá evitarse el empleo de una letra o un número aislados; también es indeseable el empleo de guiones.

7. Para facilitar la traducción y la pronunciación se emplearán de preferencia las letras "f" en lugar de "ph", "t" en lugar de "th", "e" en lugar de "ae" u "oe" e "i" en lugar de "y"; se deberá evitar el empleo de las letras "h" y "k".

8. Siempre que las denominaciones que se sugieran estén de acuerdo con estos principios, recibirán una consideración preferente las denominaciones propuestas por la persona que haya descubierto la sustancia, o la que primeramente fabrique o ponga a la venta la sustancia farmacéutica, así como las denominaciones oficialmente adoptadas en cualquier país.

9. En las DCI, la relación de grupo o parentesco (véanse los Principios Generales de Orientación, apartado 2) se indicará en lo posible utilizando una partícula común. En la lista siguiente se dan algunos ejemplos de estas partículas en relación con diversos grupos de sustancias, en particular los de nuevo cuño. Hay otras muchas partículas comunes en uso.¹ Cuando la partícula no lleva ningún guión, cabe utilizarla en cualquier parte de la denominación.

* En su 20º informe (OMS, Serie de Informes Técnicos, No. 581, 1975) el Comité de Expertos de la OMS en Denominaciones Comunes para Sustancias Farmacéuticas examina los principios generales de orientación para formar denominaciones comunes internacionales (DCI) y el procedimiento de selección de las mismas, teniendo en cuenta las novedades registradas en los últimos años en materia de preparaciones farmacéuticas. Entre las modificaciones, la más importante ha sido la extensión a las sustancias químicas sintéticas de la práctica reservada anteriormente para designar sustancias originarias o derivadas de productos naturales. Esta práctica consiste en emplear una partícula característica que indique una propiedad común a los miembros de un determinado grupo de sustancias. En el informe se examinan a fondo las razones de esta modificación y sus consecuencias.

¹ El documento de trabajo WHO/EDM/QSM 99.6, que se pone al día regularmente, contiene una lista más extensa de partículas comunes. Las personas que deseen recibirlo deberán solicitar su envío al Programa DCI, OMS, Ginebra (Suiza).

<i>Latin</i>	<i>Español</i>	
-acum	-aco	antiinflamatorios del grupo del ibufenaco
-actidum	-actida	polipéptidos sintéticos de acción semejante a la corticotropina
-adolum	-adol }	analgésicos
-adol-	-adol- }	
-astum	-ast	antiasmáticos y antialérgicos que no actúan principalmente como antihistamínicos
-astinum	-astina	antihistamínicos
-azepamum	-azepam	sustancias del grupo del diazepam
-bactamum	-bactam	inhibidores de β-lactamasas
bol	bol	esteroides anabólicos
-buzonium	-buzona	analgésicos antiinflamatorios del grupo de la fenilbutazona
-cain-	-cain-	antifibrilantes con actividad anestésica local
-cainum	-caina	anestésicos locales
cef-	cef-	antibióticos derivados del ácido cefalosporánico
-cillinum	-cilina	antibióticos derivados del ácido 6-aminopenicilánico
-conazolium	-conazol	antifúngicos sistémicos del grupo del miconazol
cort	cort	corticosteroides, excepto los del grupo de la prednisolona
-dipinum	-dipino	antagonistas del calcio del grupo del nifedipino
-fibratum	-fibrato	sustancias del grupo del clofibrato
gest	gest	esteroides progestágenos
gli-	gli-	sulfonamidas hipoglucemiantes
io-	io-	medios de contraste que contienen yodo
-ium	-io	compuestos de amonio cuaternario
-metacinum	-metacina	antiinflamatorios del grupo de la indometacina
-mycinum	-micina	antibióticos, producidos por cepas de <i>Streptomyces</i>
-nidazolium	-nidazol	antiprotazoarios del grupo del metronidazol
-ololum	-olol	bloqueadores β-adrenérgicos
-oxacinum	-oxacino	antibacterianos del grupo del ácido nalidíxico
-pidum	-prida	sustancias del grupo de la sulpirida
-pril(at)um	-pril(at)	inhibidores de la enzima transformadora de la angiotensina
-profenum	-profeno	antiinflamatorios del grupo del ibuprofeno
prost	prost	prostaglandinas
-relinum	-relina	péptidos estimulantes de la liberación de hormonas hipofisarias
-terolum	-terol	broncodilatadores derivados de la fenetilamina
-tidinum	-tidina	antagonistas del receptor H ₂ de la histamina
-trexatum	-trexato	antagonistas del ácido fólico
-verinum	-verina	esasmolíticos de acción semejante a la de la papaverina
vin-	vin- }	alcaloides de la vinca
-vin-	-vin- }	