PROPOSED INN LIST 75
INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES
WHO Drug Information

Contents

General Policy Topics
Essential drugs: looking back and exploring the future 47

Reports on Individual Drugs
An androgen contraceptive for men: preliminary findings 50
Do estrogens have antidepressant activity? 53
Rheumatoid arthritis: further exploration of combination therapy 54
Mefloquine: an update on safety issues 58
Riluzole for amyotrophic lateral sclerosis 61
Calcium channel blockers as antihypertensive agents: a need for caution 62

General Information
Peptic ulceration: revolutionary changes in management 66
Raised blood pressure in the elderly 72
Bovine spongiform encephalopathy and Creutzfeldt-Jakob disease 75
Iodized oil: recommendations to prevent iodine deficiency disorders 78
Use of vial monitors will reduce wastage of vaccine supplies 79
WHO issues new guidelines on drug donations 81

Regulatory Matters
Deadly paediatric drugs: diethylene glycol again 84
Albendazole: approved as a cysticidal agent 84
Cancer therapies: accelerating the approval process 84
Drug interactions predisposing to ventricular arrhythmias 85
PCR test approved by FDA — but only to monitor progression of HIV infection 86
Irinotecan provisionally released for metastatic colonic cancer 87
Vasopressin for enuresis: danger of hyponatraemic convulsions 88

Proposed International Nonproprietary Names: List 75 89
General Information

Peptic ulceration: revolutionary changes in management

Two decades ago, medical treatment of peptic ulceration was limited to sustained and burdensome use of antacids supplemented by anticholinergic agents and, more speculatively, changes in diet and lifestyle. Healing was an uncertain process; recurrence and relapse were common; scarring often resulted in gastric outlet obstruction; while haemorrhage and perforation were frequent life-threatening events. For many patients, elective surgery offered the only tangible prospect of relieving long-standing dyspeptic pain, or of averting major complications. However, the results of resection and restructuring were often marred by complications, including recurrence of ulceration at the gastro-enterostomy stoma.

The underlying causes of the autodigestion of the stomach lining that results in non-malignant peptic ulceration of the stomach, duodenum, or lower oesophagus remained obscure. Secretion of acid was recognized as an essential prerequisite, but whereas duodenal ulceration was shown to be strongly associated with raised or high-normal output of acid, this relationship was not found to apply to gastric ulceration which was tentatively attributed to impaired “mucosal resistance”. On the basis of these two postulated mechanisms a range of highly effective ulcer-healing drugs has been developed.

The management of these diseases has more recently been revolutionized with the discovery that much gastritis and peptic ulceration is causally associated with chronic bacterial infection. Anti-microbial therapy has become the mainstay of treatment; suppression of gastric acid production has become of secondary importance; and, for the first time, short-term therapy now holds the prospect of prolonged remission for the vast majority of patients — and at a cost that is minuscule compared to that of the prolonged maintenance therapy which was required in the past.

Antisecretory agents and other ulcer-healing drugs

The conventional ulcer-healing drugs comprise a varied array of compounds. Some, based upon chelates of bismuth (1) or aluminium (2), appear to protect the mucosal surface, either mechanically or, perhaps, by promoting secretion of prostaglandins or bicarbonate. Others, collectively described as antisecretory agents, specifically and reversibly reduce production of acid by the gastric parietal cells. These include pirenzepine — a selective anti-muscarinic agent which does not cross the blood-brain barrier and which inhibits vagally activated production of acid and pepsin at dosages which have relatively little effect on other parasympathetic functions. Similarly effective are the \( H_2 \) -receptor antagonists — cimetidine (3), ranitidine (4), famotidine (5), and nizatidine (6) — which reversibly reduce output of gastric acid by blocking histamine \( H_2 \) receptors. More recently introduced are the “proton pump” inhibitors, exemplified by omeprazole, lansoprazole and pantoprazole, which block adenosine triphosphatase-driven hydrogen/potassium exchange within the parietal cells (7). These substances are the most effective inhibitors of acid production that have yet been devised. In most, but not all studies, they have induced healing of duodenal ulcers more rapidly than \( H_2 \) receptor antagonists (7), but this advantage is less apparent in gastric ulcer (8). Omeprazole has been used with particular success in treating severe fibrosing and erosive oesophagitis (9,10), a condition in which treatment with \( H_2 \)-receptor antagonists is often disappointing (11).

The inherent limitation of monotherapy with ulcer-healing drugs — and the antisecretory agents, in particular — is that, with the exception of bismuth compounds, their effect is evanescent. Risk of relapse is reduced only for as long as maintenance therapy is continued (12). Most of the theoretical concerns regarding the safety of long-term antisecretory therapy — which included increased risk of intestinally transmitted infections, hypergastrinaemia, argyrophil-cell proliferation, carcinoid formation and neoplastic change (13, 14) — remain unconfirmed. However, the available information is incomplete: only recently has a case-control study
indicated that treatment with omeprazole is associated with a substantially increased risk of campylobacter gastroenteritis (15).

The role of \textit{Helicobacter pylori} in peptic ulceration

Fundamental therapeutic advances have been swift to follow epidemiological demonstration that — after exclusion of a substantial number of cases related to the use of anti-inflammatory drugs (16, 17) — both atrophic gastritis and peptic ulceration are strongly associated with antral infection by \textit{Helicobacter pylori} (18).

Formerly known as \textit{Campylobacter pylori}, \textit{H. pylori} is a spiral facultative anaerobic bacillus which causes chronic antral gastritis by invading the submucous layer of the gastric epithelium (19, 20). In most cases the infection remains symptomless throughout the life of the host. However, it is found in more than 90% of patients with duodenal ulcer and up to 75% of patients with gastric ulcer (18). The infection has also been associated with a tenfold increase in the incidence of precancerous metaplastic changes in the gastric mucosa (21, 22) and, far more speculatively, with coronary heart disease (23).

Diagnosis of \textit{H. pylori} infection was initially dependent upon histological examination or culture of tissue obtained by endoscopic biopsy. However, non-invasive breath tests have since been developed, which are claimed to be reliable, and which are based upon the exceptionally high urease activity of \textit{H. pylori} and the consequent formation of ammonia from urea (24).

Three lines of evidence suggest that \textit{H. pylori} infection is causally rather than opportunistically related to the majority of cases of peptic ulcer disease: the strong association between infection and ulceration (18, 25, 26); a considerable body of evidence that eradication of \textit{H. pylori} can cure gastritis (27) and markedly decrease the rate of recurrence of peptic ulcer disease (28); and evidence that an abnormally high parietal cell mass (29) and persisting \textit{H. pylori} infection subsequent to treatment (30–34) are the major determinants of both ulcer recurrence and ulcer complications.

In part, at least, it is possible that \textit{H. pylori} predisposes to peptic ulceration by increasing gastric acid output. The high basal and stimulated acid outputs of patients with \textit{H. pylori} infection and duodenal ulcer have been claimed to return to normal values after eradication of the infection (35).

\textbf{Eradication of \textit{H. pylori}}

As a result of much empirical clinical investigation it has been shown that various antimicrobial drugs possess activity against \textit{H. pylori}. Most experience has been gained with bismuth subsalicylate or subcitrate, metronidazole, tetracycline, and clarithromycin (a macrolide antibiotic). \textit{H. pylori} infection is rapidly, but temporarily, suppressed by each of these drugs but, used singly, none confers lasting and reliable elimination of infection (36–43). Moreover, resistance to metronidazole and clarithromycin — but not to bismuth compounds or tetracycline — develops rapidly during monotherapy (44).

Improved success rates (40, 45, 46) and suppression of resistance (44, 47) has been reported when these drugs are used in combination. Precise comparisons between different regimens cannot be made with confidence given a lack of prospective randomized studies. None the less, there is general agreement that “triple therapy” with bismuth subcitrate 240 mg, metronidazole 250 mg, and tetracycline 500 mg, each four times daily for two weeks combines high efficacy with low cost (48–52). Using this regimen, infection has been eliminated in 85% to 95% of cases (53). Where strains resistant to metronidazole are prevalent (47, 54), clarithromycin has been substituted with success. Amoxicillin has been substituted for tetracycline in some studies, but it seems this may result in significant loss of efficacy (49).

Many patients who have received triple therapy were treated for 14 days, but it is claimed that no clear advantage accrues from extending treatment beyond one week (49, 55, 56). This is important since about half the treated patients are poorly tolerant of the gastrointestinal disturbances — nausea, vomiting and diarrhoea — caused by metronidazole and tetracycline, and to a lesser extent by clarithromycin and amoxicillin (49, 57–59). Clarithromycin can also cause a disturbance of taste that some patients find intolerable, while bismuth subsalicylate temporarily turns the tongue and stools black (60).

Little has been published on the antimicrobial actions of either metronidazole or of bismuth subsalicylate and subcitrate in this context. The efficacy of metronidazole is predictable, since nitroimidazoles are selectively taken up by anaerobic bacteria in which they are reduced to products that disrupt DNA and inhibit nucleic acid synthesis. Quite unanticipated was the finding obtained in several independent studies that
colioidal bismuth subcitrate is as effective in the short term in healing recently-diagnosed or chronic duodenal ulcer as the H₂-receptor antagonists, cimetidine and ranitidine (1). Like salts of other heavy metals, these bismuth salts have a non-specific antimicrobial effect (61–63). It remains uncertain whether, as is often assumed, they directly protect ulcerated mucosa (64, 65) and they have more recently been accredited with other properties, any of which could provide a basis for their clinical effect. They are claimed to reduce production of pepsin, but not of acid (66); to interact with gastric glycoproteins to form a complex that inhibits a proteolytic enzyme secreted by H. pylori (67); to stimulate secretion of anti-inflammatory prostaglandins (68, 69); and to block adhesion of H. pylori to glycerolipid receptors in the gastric epithelium (67); to inhibit a proteolytic enzyme secreted by H. pylori (64).

Antimicrobials versus antisecretory agents

The results of many independent studies demonstrate that both duodenal ulcers and gastric ulcers unrelated to anti-inflammatory drugs are healed as effectively by antimicrobial therapy as by antisecretory agents. The overwhelming advantage of H. pylori eradication with antimicrobials is that a short-term treatment regimen greatly reduces ulcer relapse rates (71). This protective effect has been shown to persist in the case of duodenal ulcer for at least 7 years (72).

Antisecretory agents including omeprazole and H₂-receptor antagonists reduce relapse rates only for as long as they are given as maintenance therapy. They do not eradicate H. pylori (73, 74) and they may even aggravate the gastritis associated with antral infection (75–77). Perhaps for this reason, pretreatment with omeprazole has been shown to decrease the efficacy of anti-microbial therapy in some situations (78) but not in others (79). This disadvantage, however, has not been evident when antisecretory agents are given simultaneously with antimicrobials. Indeed, the addition of omeprazole to triple therapy has been found in several studies to improve efficacy — with cure rates rising over 95% in 7-day regimens (56, 79–81) — even in the presence of metronidazole-resistant strains (56, 81).

The somewhat marginal advantages gained by adding an antisecretory agent to the basic “triple therapy” increases the daily drug costs by some tenfold (60). The American College of Gastroenterology has suggested that these more costly regimens might be reserved particularly for refractory or large H. pylori-positive ulcers (52). The US Food and Drug Administration has recently approved a combination of clarithromycin with omeprazole for eradication of H. pylori. This regimen, it has been noted (60), offers no advantage in effectiveness over less expensive combinations. It may, however, be better tolerated than multiple antibiotic regimens, and the smaller number of tablets required may improve compliance.

Clinical management of peptic ulceration and dyspepsia

The American College of Gastroenterology has recently issued a consensus statement (52) which concludes that antimicrobial therapy is now indicated for all H. pylori-infected ulcer patients. Given the very high prevalence of H. pylori infection in patients with uncomplicated duodenal ulcer, and the substantial incidence of false-negative results obtained with the currently available routine diagnostic tests for H. pylori (24), it concludes that empirical treatment — given without demonstration of infection — is warranted in this situation.

In contrast, the statement underscores the need always to exclude the possibility of malignant ulceration by direct endoscopic inspection and biopsy before treating even benign-appearing gastric ulcers (82, 83) and to ensure that these patients are followed up until it is evident that they have responded well to antimicrobial therapy.

Advice on the management of new-onset dyspepsia is less precise because adequate comparative data are not available on the various options (84, 85). Nonsteroidal anti-inflammatory drugs, if they are being taken, should be withdrawn at least for a trial period pending reassessment. Immediate endoscopic or radiological investigation should be proposed to any patient in whom there is suspicion of gastric malignancy, including all patients aged over 50 years (86). However, for younger patients who test positive for H. pylori infection in a non-invasive test, a trial of antimicrobial therapy is proposed as a cost-saving option, since full investigation can then be directed only to those patients whose symptoms subsequently recur (87, 88).

It is acknowledged, however, that the response to antimicrobials in dyspeptic patients without a demonstrable ulcer is unpredictably variable (89). Empirical antimicrobial therapy for dyspeptic symptoms without H. pylori testing is strongly
discouraged, particularly where the prevalence of *H. pylori* infection is relatively low among younger dyspeptic patients, on the grounds that the treatment is not always well tolerated, and that widespread and indiscriminate use of antibiotics favours the emergence of resistant organisms.

**Towards the development of a vaccine**
Yet another step aimed to simplify and enhance protection against *H. pylori* infection is now well advanced. Phase II studies of an oral vaccine intended to prevent reinfection and to stimulate immunity in uninfected persons are now in progress both in Switzerland and in the United States (90). The product contains a purified urease antigen produced from a cloned *H. pylori* urease gene together with a mucosal adjuvant. Oral immunization is reported to have consistently protected animals against infection and to have cured established infections. The hope is that, in due course, it will become available for routine use and provide a high degree of protection against gastric carcinoma as well as peptic ulceration.

**References**


General Information


**Raised blood pressure in the elderly**

The management of raised blood pressure in the elderly continues to generate discussion and divide opinion. It is still widely believed that in older age groups hypertension runs a relatively benign course (1). There is also well-founded concern that, in the presence of significant atherosclerotic disease, any attempt to reduce blood pressure may compromise cerebral blood flow and trigger postural hypotension or ischaemic stroke (2, 3).

None the less, objective evidence generated in recent years consistently shows that, on balance, the benefits which derive from treating high blood pressure in the elderly decisively outweigh the risks (4). Major randomized prospective trials have consistently demonstrated that treatment of moderate hypertension in elderly patients reduces overall risk of cardiovascular complications (5–8). This benefit is even discernible in official US statistics which show that, throughout the 1980s, the steepest decline in cardiovascular deaths occurred among patients aged over 75 years (9).

A prime objective in treating moderate hypertension in older patients is to protect them against atherothrombotic cerebrovascular disease. Hypertension has been estimated to contribute to more than
three-quarters of the 400 000 cases of stroke recorded annually in the United States (10). This association has recently been explored prospectively within a large collaborative programme in which 45 prospective cohorts involving some 450 000 individuals have been followed over periods ranging from 5 to 30 years (11). Analysis of over 13 000 strokes recorded within these cohorts, most of which have been fatal, has confirmed that diastolic blood pressure is a major determinant of stroke, and that this relationship shows no attenuation at pressures below 80 mmHg. Whereas the relation was found to be strongest among younger individuals, it remained highly significant among those aged over 65.

This analysis does not exclude isolated systolic hypertension — a condition resulting from decreased elasticity of the arterial tree which becomes increasingly prevalent with age (12, 13) — as a significant risk factor. In a 5-year trial involving nearly 5000 patients aged over 60 years with this type of hypertension, stepped antihypertensive therapy reduced the death rate from all causes by some 13% (14). The incidence of stroke among treated patients was reduced by more than one-third. In absolute terms this represented, for every 1000 treated patients a decrease of 30 cerebrovascular incidents over the 5-year period.

Since the risk of stroke is greatest in old age, the results of these studies persuasively support the case for controlling both diastolic and systolic hypertension in this age group. It is acknowledged that broad generalizations must be guarded since the risk of stroke varies widely between different populations (15), and because other factors, including serum cholesterol concentrations, have relevance (16–22). Further insight into the relationship between blood pressure and stroke within different age groups and different populations will be forthcoming from an ongoing review of published randomized trials of blood pressure reduction (11). However, there is no reason to believe these results will compromise the general rule that control of blood pressure is the most effective means of reducing the risk of stroke.

In contrast, it remains uncertain whether effective control of blood pressure offers comparable benefit in reducing the risk of dementia. It is reasonable to assume the existence of such benefit on the grounds that hypertensive cerebrovascular disease is a determinant of many cases of dementia (23, 24). On the other hand, reduction of blood pressure, particularly in the presence of arteriosclerotic disease, could possibly exacerbate progression of dementia as a result of inadequate perfusion during episodes of hypotension (25).

The extensive Framingham population study undertaken in the United States has favoured the first of these hypotheses. It has demonstrated a modest long-term association between increasing blood pressure and subsequent incidence of dementia (26, 27), which was most marked among persons who remained untreated (27). In contrast, in a large multicentre trial conducted in the United Kingdom, treatment of moderate hypertension in elderly patients was without discernible influence over a period of 4–5 years on any measure of cognitive function (28). It is possible that benefit might have emerged over a longer period of treatment, or that these patients had been rendered unresponsive as a result of diffuse arteriosclerotic disease. However, the results of a more recent population study reported from Copenhagen (29) suggest that any benefit deriving from antihypertensive therapy could be masked because, it is claimed, blood pressure may be lowered as a consequence of pathological processes associated with dementia.

In this latter cross-sectional, population-based study (29), both systolic and diastolic blood pressure were inversely related to prevalence of dementia in elderly people. Because this totally unanticipated relation was strongest in persons with prolonged or severe dementia, the authors suggest that low blood pressure is more likely to be a consequence rather than a cause of dementia. To support this idea they point to evidence indicating that blood pressure falls during the course of Alzheimer’s disease (30) — a feature variously attributed to changes in autonomic function and other characteristics of the disease (30–35) — and that this fall may contribute to the dementia by reducing cerebral blood flow (36).

This is an attractive hypothesis since it implies that a common unidentified factor may contribute to the progression of both Alzheimer’s disease and vascular dementia. Firstly, however, there is a need to understand why dementia should be associated with raised blood pressure in Framingham and with low blood pressure in Copenhagen. Inconsistencies between results obtained in major epidemiological studies sometimes reflect subtle differences in design and execution, but every effort should always be made to explain them. In this instance, investigation of the inconsistency may simply underscore the need for confirmatory studies, but it
may also supply leads for new avenues of investigation. For the present, the important message is that neither in Framingham nor in Copenhagen was there any evidence that anti-hypertensive therapy induced or intensified any measure of dementia. The principle that favours the prudent reduction of raised blood pressure in elderly subjects has lost none of its validity.

References


**Bovine spongiform encephalopathy and Creutzfeldt-Jakob disease**

The possibility that another infectious disease has crossed the interspecies barrier from an animal reservoir to man has once again created headline news (1). In this instance the disease is chronic, disabling and ultimately fatal, and the reservoir of infection is contained in cattle intensively bred for food production. The identification of a new variant of Creutzfeldt-Jakob disease (V-CJD) in 10 patients in the United Kingdom (2) has been linked — thus far, on the basis of circumstantial evidence — to the emergence of a bovine spongiform encephalopathy (BSE) among cattle in the UK (3). This latter disease, which has become widespread within the British herd, was first identified in 1986 and subsequently attributed to recycling of bovine material in concentrate feed back to cattle — a practice that was banned in Britain in July 1988. The frequency with which new cases are reported has since declined significantly in the UK (4), but others are now reported sporadically, although in much smaller numbers, from other European countries.

No epidemiological link has previously been described to suggest that human disease has been caused by any of the spongiform encephalopathies known to be transmissible within specific animal species (5). Indeed, it has been pointed out that the scrapie agent, endemic for almost 300 years among sheep in the UK, has posed the same threat to the food chain over many generations, but without detectable risk to consumers (4). Conclusive proof that the recent emergence of V-CJD within the British population was triggered by exposure to BSE remains outstanding (6). None the less — given that none of the available food-processing technologies (domestic cooking, pasteurization, sterilization, freezing, drying, irradiation, acidification, fermentation and pickling) is fully effective in inactivating the infectious agent — both the British Spongiform Encephalopathy Advisory Committee (3) and, more recently, WHO (7), have advised that cross-species transmission of the disease to man from the known pool of diseased cattle must be accepted as a working hypothesis.

Stringent culling policies aimed to eliminate BSE from beef and dairy herds as rapidly as possible are now generally regarded as crucial to the restoration of consumer confidence in beef products. It is possible that British animals now developing signs
of the disease may have been exposed to residual supplies of contaminated feed long after the 1988 ban was imposed. However, since the alternative possibility that the disease has become endemic in infected herds as a consequence of vertical or horizontal transmission has not been entirely excluded, an extensive culling programme now being planned will accommodate this possibility. Regardless of whether the evidence ultimately proves or refutes an association between BSE and V-CJD within the context of the current epidemic, the properties of the group of subviral transmissible agents, or prions (6, 8–10), known to be associated with these diseases is likely to demand continued long-term monitoring. The prion protein, which comprises a modified form of a normal host-encoded glycoprotein (11) is exceptionally resistant to heat, ultraviolet and ionizing radiation, and chemical disinfectants but, like viruses, it shows strain variation and mutation. Some strains have been associated with other transmissible spongiform encephalopathies (12) including rare human diseases such as kuru (formerly transmitted during cannibalistic rituals among the Fore peoples in Papua New Guinea), scrapie in sheep and encephalopathy in mink. All are neurodegenerative conditions that are transmissible to experimental animals following inoculation or dietary exposure. The causative agents must consequently be regarded as sharing a general potential to cross species barriers. As yet, however, CJD and scrapie are the only transmissible spongiform encephalopathies that are known to exist as an endemic infection of their natural hosts.

The identification of the prion as modified naturally-occurring cellular protein sets CJD apart from all other known transmissible diseases of man. Characterized by rapidly progressive dementia, myoclonus and a characteristic electroencephalogram (13, 14), the disease was first recognized as an inherited autosomal dominant disorder. Latterly, it has been associated with a point mutation or insertion in the prion protein gene (10). Many cases, however, have been described as arising sporadically without known cause, while the potential for transmission had to await documentation of cases of CJD among patients who have received human grafts of dura mater or cornea, or injections of human pituitary-derived growth hormone (15, 16) or gonadotrophin (17, 18). The paradoxical observation that a disease can be genetically inherited, transmitted and also occur sporadically has been hypothetically explained on the basis that “a post-translational change in protein structure (in this case, the prion protein) can be pathogenic, either by loss or gain of function, and can act as a template to induce a similar change in the normal cellular form of the protein” (19).

Individuals homozygous for a common polymorphism at codon 129 of the prion protein gene have been shown to be particularly vulnerable to both the sporadic and iatrogenic forms of the disease (20, 21). Unexpectedly, none of the patients in the UK who have died with the newly defined variant of CJD possessed this genotype. These cases were also distinctive in that the patients were atypically young. Some were still in their teens, whereas CJD typically presents in patients over 60 years. The neuropathological changes, which included extensive kuru-like amyloid plaques in the cerebellar lobes and a unique pattern of prion protein immunostaining, were also highly distinctive (2). Much effort will now be directed to determining whether or not the single prion strain that has been associated with BSE in cattle — and which rarely undergoes phenotypic change following passage in other species — (22) is also associated with human CJD variant.

Given the possibility of iatrogenic parenteral transmission of infection, specific measures have been recommended over the past few years to assure the safety of bovine tissues needed in the production of medicinal products (23). These include calf serum contained in media for growing cells used in vaccine production, pancreas required for bovine insulin, and lung and gut which are the source of heparins. Relevant guidelines were first developed by the UK Committee on Safety of Medicines in 1989. In 1992, these were adopted essentially unchanged by the European Committee for Proprietary Medicinal Products (24) and recommended for use by WHO (25). Similar requirements have been introduced in other countries. Most stringent are those adopted by the US Food and Drug Administration (26). In 1993 the agency advised manufacturers that bovine materials derived from cattle that have originated or resided in countries where BSE has been diagnosed should not be used in any product regulated by the agency that is intended for administration to human beings. A list is maintained by the agency of countries where the disease is known to exist, and manufacturers of products that contain bovine material are asked:

• to obtain from suppliers information on all countries in which the animals were reared, and relevant inspection certificates of slaughter; and
• to maintain within batch records at the site of manufacture, details of each lot of bovine material used, and each lot of any regulated product — whether or not it is approved at the time of manufacture — in which the material has been incorporated.

The regulations that apply throughout the European Union derive from two principles: exclusion of cattle with a history of exposure to BSE as a source of starting materials and, when applicable, preferential use of purification procedures shown to be most efficient in inactivating or eliminating transmissible agents.

Specifically, all materials destined for pharmaceutical products are required to be obtained from cattle aged less than six months that have been born and reared in countries where adequate surveillance and reporting requirements are in place; where there have been few, if any, reports of the disease; and where all affected animals and their progeny have been destroyed. These requirements apply even to the manufacture of lactose from milk, a body fluid in which detectable infectivity has not been recorded (27). They also apply to the manufacture of substances which can be subjected to efficient purification procedures without denaturing the finished product. Among these are gelatine, extracted from skin and bones, from which capsule shells are extensively manufactured, and tallow — a product of rendered bovine carcasses from which lipid substances, including triglycerides, glycerol, and sorbitan esters, are derived (3, 7).

The guidelines stress that the following methods of purification should be preferred whenever they are feasible:

• autoclaving (preferably at 134–138 °C for 18 minutes for porous-loading autoclaving, and at 132 °C for 1 hour for gravity-displacement autoclaving);
• treatment with sodium hydroxide (preferably a molar solution for 1 hour at 20 °C);
• treatment with sodium hypochlorite (preferably a solution containing at least 2% available chlorine for 1 hour at 20 °C).

Published evidence indicates that these methods are more efficient than those based upon extraction by organic solvents; removal of protein by precipitation, ultracentrifugation or adsorption; preparation of filtrates; or passage through chromatographic columns (28–30).

Meanwhile, basic research has advanced to a degree that may fundamentally extend knowledge regarding the physiological and pathological significance of prion proteins. Particularly significant is the availability of transgenic strains of mice developed to express human prion protein, and which are susceptible within a short incubation period to a range of pathogenic human prion isolates (31). Not only may this model serve to identify and characterize strains in animal reservoirs that are capable of causing CJD (32), it may also contribute to an understanding of other degenerative diseases of the central nervous system, including the highly prevalent Alzheimer’s disease which is characterized histopathologically, like CJD, by diffuse deposits of abnormal b-amyloid protein (33).

References


**Iodized oil: recommendations to prevent iodine deficiency disorders**

In the light of advice from a technical advisory group and with the approval of the International Council for Control of Iodine Deficiency Disorders, WHO has issued a statement (1) which recommends the use of iodized oil in public health programmes to prevent iodine deficiency in pregnant women — and cretinism and neonatal hypo-
thyroidism in their children — in countries or areas where the following criteria apply:

- the prevalence of iodine deficiency disorders is moderate to severe;
- cretinism and neonatal hypothyroidism are known to occur; and
- iodized salt is not available or its supply has been significantly disrupted.

It is recommended that the selected dosage schedule should be the lowest that will assure protection throughout pregnancy and for at least one year postpartum. Administered to a pregnant woman, an intramuscular dose containing some 480 mg iodine — or an oral dose containing 300 to 480 mg iodine — is cited as providing adequate protection for at least one year.

To ensure the efficiency and effectiveness of individual programmes, the organization of a monitoring system is proposed that covers logistic aspects as well as biological responses.

Process indicators should include assessment of:

- availability of iodized oil at distribution points;
- the system for registering and tracking the doses given;
- the proportion of eligible women who receive iodized oil during antenatal care; and
- the system for determining the outcome of pregnancies.

Optimally, the following biological variables should be monitored in sufficient individuals to provide an accurate assessment of trends:

- in infants: birth weight, perinatal death, circulating concentrations of neonatal thyroid-stimulating hormone (TSH);
- in mothers: urinary iodine concentration, breastmilk iodine concentration.

Monitoring of neonatal TSH and/or maternal urinary iodine is regarded as particularly important, since these variables provide the most direct information on dose/response relationships.

The supply of thyroid hormone to the human fetus appears to be critically dependent on maternal thyroid status during the first trimester of pregnancy. The aim, therefore, is to administer iodine as early as possible during the course of pregnancy. Indeed, full protection can be assured only when iodine deficiency is corrected prior to conception. It has been established that this protection is assured in non-pregnant fertile women who receive, every three months, 100 to 200 mg iodine in a single oral dose (2).

WHO concludes that, based on available evidence, there is no reason to believe that iodized oil given, as recommended, either before or at any stage of gestation, exposes either the mother or the fetus to any hazard from iodine overload (2). On the contrary, correction of iodine deficiency not only protects infants from endemic cretinism and mental retardation, it has also been shown to increase birth weight and to decrease fetal and perinatal mortality.

References


Use of vial monitors will reduce wastage of vaccine supplies

Global immunization programmes use about 2.5 billion doses of vaccines every year which are purchased at a cost of some US$ 90 million. WHO's Global Programme for Vaccines and Immunization has recently issued policy guidelines which it is believed could reduce unnecessary rejection of vaccines used in national vaccination programmes by as much as 30%. If this target is reached, considerable savings will be achieved.

At present national recommendations for handling vaccines have been very conservative to ensure protection from the harmful effects of heat — the main cause of loss of potency in these products. Health workers have been trained to discard all vaccines after a break in the cold chain, even if the break is only suspected. If a health centre refrigerator malfunctions overnight, the vaccine is rejected as soon as the problem is discovered. In some centres health workers are instructed to
discard all vaccine that has been taken into the field twice without being used, even if it seems that the cold chain has been scrupulously maintained.

These precautions against possible heat damage have inevitably resulted in the loss of large quantities of vaccines arbitrarily deemed as unusable. However, the recent development of chemical systems that gradually change colour during exposure to heat has provided the basis for manufacturing “vaccine vial monitors” — heat-sensitive materials applied to vials which, by progressive and irreversible colour change, register cumulative heat exposure over time. Monitors, approved by WHO on the basis of extensive laboratory testing, are manufactured in batches that are specific for a given vaccine. The rate at which the colour of the monitor changes is thus adjusted to the known heat-sensitivity, and hence indirectly to the stability of the vaccine. The reliability of the system is assured by testing samples from each batch of monitors before shipment.

This correlation between colour change and heat-sensitivity is assured to a degree that will permit health workers to use vaccines throughout their stable storage life. It is also important to appreciate that, independently of heat exposure, all vaccines gradually degrade with time even under correct storage conditions. Consequently, no product should ever be used after it has passed its labelled expiry date, regardless of the colour of the monitor.

This new system complements and does not replace the cold chain monitor card that is currently packaged with each consignment of vaccine supplied by UNICEF. The card indicates when and where the upper temperature limit of the cold chain has been surpassed, while the vial monitor shows the cumulative impact of these perturbations on the product. The cold chain monitor is a useful managerial tool for checking shipments of vaccine on arrival at central and peripheral stores and may be used to conduct national cold chain surveys. However, it is the vial monitor and the expiry date that provide ultimate guidance on whether the contents of a vial may be used.

Even after the introduction of vial monitors it will still be necessary to discard all opened vials of some attenuated vaccines, including measles, yellow fever and BCG, at the end of each immunization session. However, the possibility of using opened vials of oral polio vaccine, diphtheria/tetanus/pertussis, tetanus toxoid and hepatitis vaccines to be used in subsequent immunization sessions until a new shipment of vaccine arrives can create substantial savings. This change in procedure demands strict discipline. It is vital that every time, before an opened vial is re-used, the following conditions are met:

- the expiry date has not been passed;
- the vaccine has been stored under appropriate cold chain conditions (0–8 °C);
- sterile procedures have been fully observed;
- there is no suspicion that the opened vial has been contaminated;
- there is no visible evidence of contamination; and
- all vials of vaccine that are taken from and opened outside the health centre are discarded at the end of the day.

This, however, is only applicable to vaccines that meet WHO requirements for potency and temperature stability, that are packaged according to ISO standards, and — in the case of injectable vaccines — contain an appropriate concentration of thiomersal or other preservative. All vaccines supplied by UNICEF meet these requirements.

Extensive training in the reading and interpretation of monitors must precede their introduction. This effort needs to be directed not only to cold room personnel but to staff responsible for vaccine storage and handling at each point in the distribution chain from the central store to the peripheral health centres. Health workers responsible for administering vaccines should learn to check each vial monitor before using the contents, and to report to their supervisors any vial bearing a monitor indicating that it should be rejected or that is damaged in any other way.

Monitors are already being attached to vials of oral polio vaccine — which has the least resistance to exposure to heat — and they will appear on vials of other vaccines distributed by UNICEF in due course. It is anticipated that the savings resulting from unnecessary rejection of vials will, in general, greatly exceed the small cost of attaching the monitors. In the short term, however, particularly where the cold chain is poorly maintained, rejection rates may rise above current levels because use of monitors will result in recognition of stocks that should be discarded.

The introduction of the monitors will not only serve to reveal these deficiencies, it will also provide the
means to review them and to correct them. Moreover, if training can ensure that everyone handling vaccines will discard vials as soon as the monitors have reached their end-point, immunization sessions can be planned more flexibly, since vaccines can be temporarily removed and restored to the cold chain at any stage of distribution for as long as the monitor does not indicate that they should be discarded. Managerially, of course, it is important to maintain all vials of vaccine within the cold chain for as long as possible in order to ensure maximum viable life in the field. Given this general proviso, a policy permitting the use of monitored vials outside the cold chain is best limited to specific circumstances including use in remote inaccessible areas, during cool seasons, or during national immunization days.

Aside from permitting more flexible use of vaccines, monitored vials assist in the routine management of the cold chain. Vials approaching their endpoint can be preferentially selected for routine use before those with a longer remaining shelf-life. Conversely, vials with least exposure to heat can be preferred for use in remote centres or by mobile teams. Unanticipated colour changes in monitors, like unexpected readings on refrigerator thermometers, provide an indication or confirmation of a cold chain problem and may help to identify its cause. Thorough training of staff in the use of monitors may enable the classic “first-in, first-out” policy to be modified with advantage in smaller stores. In larger stores, however, where vaccines remain in cartons it may be impractical for the storekeeper to pick out vaccines for immediate use on the basis of colour changes on vial monitors. In these circumstances, the classic rotation policy is likely to remain the most appropriate management option.


WHO issues new guidelines on drug donations

Medicines are an essential component of health care everywhere, not least where natural disaster, famine, armed rebellion or civil strife mobilize external humanitarian support. Relief efforts are impeded and even disrupted, however, if the drugs that arrive amid the confusion and danger inherent in these situations are either irrelevant to local needs or, for one reason or another, unusable. Anyone who doubts that serious disruption and frustration can result from unsolicited gifts of such drugs should refer to the examples featured in WHO’s recently issued Guidelines for Drug Donations (1):

- 50 persons needed six months to sort 5000 tons of drugs and medical supplies sent to Armenia following the 1988 earthquake. The labelled shelf-life of some of the drugs had already expired on arrival. Others were destroyed by frost. Less than half were relevant to emergency needs (2).

- Seven truckloads of time-expired tablets of acetylsalicylic acid took six months to burn in war-torn Eritrea. 30 000 bottles of time-expired aminoacid infusion had to be dumped far away from human settlements “because of the smell” (3).

- Contact lens solutions, appetite stimulants, lipid lowering agents and expired antibiotics were contained in a large consignment of assorted packets of drugs sent to a devastated area of southern Sudan. All were labelled in French, a language unknown locally (4).

- An 8-ton consignment received in Guinea Bissau contained 22 123 packages of 1714 different products which “greatly interfered with government efforts to rationalize drug supply and drug use” (5).

- Of all drug donations received by the WHO field office in Zagreb, Croatia, in 1994, 15% were unusable, and 30% were not needed (6). At the end of 1995, stores in Mostar, Bosnia, contained 340 tons of time-expired drugs (7).

In the midst of an emergency situation the arrival of large quantities of randomly-assorted medicines, which may have no relevance to the situation, will distract overworked health professionals from vital tasks; handling costs — which include import taxes and overheads for storage and distribution — are likely to exceed the value of the donation; while drugs that are degraded or inadequately labelled will add yet another dimension to the health risk (8). To avoid these frustrations, a sound analysis of the needs must be made on the ground as a matter of highest priority; donations should be based on these expressed needs; and unsolicited drug donations should be discouraged, with the possible exception, in acute emergencies, of items that are included in the UN list of emergency relief items (9).
The following 12 articles, which are further annotated and qualified within the guidelines, are based on four principles: donations should be of maximum benefit to the recipient; they should respect the requirements of the recipient; there should be no double standards in quality; and there should be effective communication between donor and recipient.

**Selection of drugs**

1. All drug donations should be offered in response to an expressed need and be relevant to the disease pattern in the recipient country. Drugs should not be sent without prior consent by the recipient.

2. All donated drugs or their generic equivalents should be approved for use in the recipient country and appear on the national list of essential drugs, or, if a national list is not available, on the WHO Model List of Essential Drugs (10), unless specifically requested otherwise by the recipient.

3. The presentation, strength and formulation of donated drugs should, as far as possible, be similar to those commonly used in the recipient country.

**Quality assurance and shelf life**

4. All donated drugs should be obtained from a reliable source and comply with quality standards in both donor and recipient country. The WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce should be used (11, 12).

5. No drugs should be donated that have been issued to patients and then returned to a pharmacy or elsewhere, or that have been given to health professionals as free samples.

6. Upon arrival in the recipient country all donated drugs should have a remaining shelf-life of at least one year.

**Presentation, packaging and labelling**

7. All drugs should be labelled in a language that is widely understood by health professionals within the recipient country; the label on each individual container should at least contain the International Nonproprietary Name (INN, or generic name), batch number, dosage form, strength, name of manufacturer, quantity in the container, storage conditions and expiry date.

8. As far as possible, donated drugs should be presented in large quantity units and hospital packs.

9. All drug donations should be packed in accordance with international shipping regulations, and be accompanied by a detailed packing list which specifies the contents of each numbered carton by INN, dosage form, quantity, batch number, expiry date, volume, weight and any special storage conditions. The weight per carton should not exceed 50 kilograms. Drugs should not be mixed in the same carton with other supplies.

**Information and management**

10. Recipients should be informed of all drug donations that are being considered, prepared or actually in transit.

11. In the recipient country the declared value of a drug donation should be based on the wholesale price of its generic equivalent in the recipient country or, if this information is not available, on the wholesale world-market price for its generic equivalent.

12. Costs of international and local transport, warehousing, port clearance and appropriate storage and handling should be paid by the donor agency, unless specifically agreed otherwise with the recipient in advance.

These guidelines were approved, in principle, by the World Health Assembly in May this year, on the understanding that experience of their use over the next 12 months will be reviewed in collaboration with all interested parties (13).

**References**


Regulatory Matters

Deadly paediatric drugs: diethylene glycol again

Haiti — An Associated Press report widely featured in national newspapers on 4 July of this year implicates diethylene glycol, yet again, in the fatal poisoning of children.

The deaths of more than 50 pre-school children in Haiti from acute renal failure have been attributed to two locally-fabricated (and possibly counterfeit) liquid paediatric formulations of an antipyretic medicine. The Minister of Health is reported to have ordered the immediate destruction of all stocks of these products which are presumed to have been formulated with diethylene glycol, a highly toxic industrial solvent.

WHO has responded by sending dialysis equipment vital to the treatment of surviving children, and US nephrologists are on the ground assessing the situation and further investigating its causes.

Concerns have been expressed that the quality of locally manufactured pharmaceutical products is inadequately controlled. Deaths from renal failure have been attributed to use of diethylene glycol as a solvent in medicinal products in the United States in 1937. This resulted in legislation which set in place many of the basic tenets of drug regulation now enforced by the US Food and Drug Administration. In recent years, similar tragedies have been reported from Argentina, Bangladesh, India and Nigeria.

Until effective international initiatives are forthcoming — including the organization of a pool of technical support to advise small companies in less developed countries on the basic principles of quality assurance — further such catastrophies must be inevitable.

Albendazole: approved as a cysticidal agent

United States of America — The Food and Drug Administration has recently accorded “orphan drug” status to the anthelminthic drug, albendazole (Albenza®, SmithKline Beecham), for treatment of neurocysticercosis and hydatid disease (1). The first of these diseases is acquired by ingestion of pork tape worm (Taenia solium) eggs in contaminated food or water. The second results from ingestion of eggs of one of two species of the Echinococcus tapeworm, which in North America is rarely harboured by dogs.

The agency estimates that, in patients with active neurocysticercosis, albendazole is active in 40 to 70% of cases, whereas it eliminates hydatid cysts in some 30% of patients and reduces their size in an additional 40%.

Impaired liver function, leukocytosis, and nausea/vomiting are cited as the most significant adverse systemic effects of albendazole. In patients with neurocysticercosis, oedematous inflammatory reactions are liable to induce headache, while abdominal pain is frequently reported by patients treated for hydatid disease.

The treatment of neurocysticercosis, which is highly prevalent in some developing countries, has been discussed in extenso in an earlier issue of this journal (2).

References

Cancer therapies: accelerating the approval process

United States of America — Until now, the Food and Drug Administration has usually required evidence of improvement in survival time or quality of life before approving a proposed new cancer therapy. However, in order to accelerate access to promising new treatments, and after wide consultation with groups representative of patients, physicians, the pharmaceutical industry, and the research community, it has been decided that the following four initiatives will be adopted:
• approval time will be shortened by accepting evidence of tumour shrinkage as an early indicator of effectiveness;

• collaboration will be established with pharmaceutical companies to enable promising cancer therapies approved by other countries to be made available to cancer patients before the product is approved in the United States;

• all FDA advisory committees concerned with cancer therapy will now include an ad hoc member “who has personal experience with the illness for which a new product is being considered”;

• administrative procedures will be changed to facilitate the investigation of new uses for cancer therapies already marketed in the United States.

These changes will not waive the responsibility of sponsoring companies to provide data relating to survival and quality of life after the product has been marketed. Approval may be withdrawn if postmarketing studies fail to demonstrate clinical benefit.

The possibility of extending such initiatives to therapies for patients with other serious and life-threatening conditions is under consideration.


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**Drug interactions predisposing to ventricular arrhythmias**

**United States of America/United Kingdom** — Between 1990 and 1992, doctors in the United States (and subsequently in other countries) were alerted on several occasions to the finding that two non-sedating antihistamines, terfenadine (Seldane®; Hoechst Marion Roussel) and astemizole (Hismanal®; Janssen) could induce electrocardiographic changes, including prolongation of the QT interval, cardiac arrest, torsades de pointe and other ventricular arrhythmias when the maximum recommended drug plasma concentrations are exceeded (1–4). Blood concentrations of these drugs, it was noted, were greatly increased in individual patients who had concomitantly taken either a macrolide antibiotic (erythromycin or troleandomycin), or the imidazole systemic anti-fungal agent, ketoconazole (3, 4). Doctors were advised to avoid prescribing these drugs to all patients taking non-sedating antihistamines.

Now, a similar warning has been issued in respect of cisapride (Prepulsid®; Janssen), a neuroleptic agent which is used primarily to reduce gastric stasis associated with diabetes and other causes of neuropathy of the autonomic system. When used alone, cisapride has not been associated with serious adverse effects. However, there is now evidence that, when imidazole antifungal drugs or macrolide antibiotics are taken concomitantly, plasma concentrations of cisapride rise and electrographic changes develop that predispose to ventricular arrhythmias (5).

A review of data relevant to cisapride has recently been provided by the UK Committee on Safety of Medicines (6). Some 25 cases of ventricular arrhythmia (of which two were fatal) have been reported worldwide in patients who have received antifungals or macrolide antibiotics while on cisapride. These cases, characterized by prolongation of the QT interval, torsades de pointes and/or ventricular fibrillation, have been associated with erythromycin (ten reports), flucloxacilone (nine), clarithromycin, (four), ketoconazole (two), itraconazole (two) and miconazole (one). In three instances individual patients received two of these drugs.

Most of these patients were also receiving other medicines and some had predisposing conditions including hypokalaemia. It is notable that the plasma concentration of cisapride was raised in three of four patients in whom it was measured, and that no reports of prolongation of the QT interval have been reported in patients taking cisapride alone.

The Committee has consequently recommended that:

• cisapride should not be co-administered with oral or parenteral formulations of the antifungals and antibiotics cited above.

• its use should be carefully considered in patients found to have a prolonged QT interval, whether this is related to a congenital syndrome or acquired as a result of electrolyte disturbances or other medication.

• the recommended maximum starting dose (40 mg daily) should not be exceeded.
In a broader context, these findings point to a need to review the possibility that other drugs extensively metabolized in the liver may interact adversely with imidazole antifungals and macrolide antibiotics.

More fundamentally, a study focused on terfenadine has recently illustrated the difficulty of ensuring that official messages regarding serious drug interactions are recalled and heeded by health professionals in the course of their routine duties (7). In the USA, starting in 1990, all practising doctors have received two letters alerting them to the problem, the product labelling has been revised to include a prominent warning, and case reports, warnings, commentaries, and clinical investigations have been reported in widely circulated journals. None the less, it is estimated that, during the first half of 1994, some 2–3% of several millions of persons in the USA who used terfenadine were likely to have taken either a macrolide antibiotic or an imidazole antifungal during this time (7).

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**PCR test approved by FDA — but only to monitor progression of HIV infection**

**United States of America** — The Food and Drug Administration has announced its first approval (1) of a polymerase chain reaction (PCR) test Amplicor HIV-1 Monitor Test®; Roche Diagnostic Systems Inc.) for directly detecting proviral HIV-1 genetic material in peripheral blood mononuclear cells through a gene amplification technique (2).

Both the sensitivity and the selectivity of the test are considered to be high. Blood samples containing more than 800 copies of the target genetic material have been detected with 100% reliability in pre-marketing studies, and none of 495 samples from known HIV-1 negative donors tested false-positive.

At present, the test is approved only for predicting the risk of disease progression in HIV-infected patients. It is not labelled for use as a screening or confirmatory test for HIV infection. Two small clinical trials have indicated that if viral levels (as measured by the PCR DNA) are high prior to treatment, or if they increase by five-fold or more during the first eight weeks of therapy, the risk is high of further progression to AIDS, an AIDS-related infection, or death. Serial PCR tests undertaken on patients receiving combinations of antiretroviral drugs have demonstrated progressive reduction in the viral load but, as yet, these changes have not been related to clinical responses in drug therapy.

On grounds of cost alone, PCR tests are impractical to use for screening purposes. Prices charged for tests as yet unapproved for routine clinical use within the USA range from $125 to $200 (3). In contrast, most HIV serological screening tests — which detect antibodies to HIV and which have comparable sensitivity and specificity — cost as little as $1 to $2 to perform (4). Most of these latter tests are enzyme-linked immunosorbent assays (ELISAs) which require up to 3 hours to perform. Others, however, are simple agglutination and microdot assays which can be read within a few minutes, require little equipment, and are particularly appropriate for field testing in developing countries (5).

A particularly important potential application for PCR tests is in the early diagnosis of HIV infection in neonates and infants (3) since HIV serological tests are uninformative during the first year of life (6). As yet, however, the reliability of PCR tests in this setting remains uncertain. In some of the earlier published studies, unacceptable incidences of false-positive and false-negative results were reported (7, 8), and a recent multicentre quality control study suggests that low but clinically significant rates of false-positive and false-negative results continue to occur (9).
At present, within many clinical studies conducted in the USA, a working definition is used for the
diagnosis of vertical HIV infection which requires that positive results be obtained from two separate
blood samples, one by HIV culture (which is slow, labour intensive and expensive) and the other by
culture, by PCR, or (in infants aged more than 4
weeks) by neutralizable plasma p24 antigen (9).

There is now a call to develop an alternative
strategy, derived on evidence that approximately
30% to 50% of infected infants are positive at birth
to PCR testing, and that most of the remainder
become positive within seven days (10). The
proposal is that infants at risk should be screened
by PCR testing at birth and, as necessary, weekly
thereafter during the first month of life, and that
confirmatory testing be undertaken on those found
positive (6). This strategy seeks to establish a
diagnosis as rapidly as possible in order that antiviral therapy can be started at an early stage of
viral replication and before opportunistic infections
develop.

However, recent evaluations of sequential and
combination test strategies suggest that PCR
results during the first month of life are of value
primarily if the test is negative (11), that a single
PCR test is not sufficient to diagnose or exclude
HIV infection, and that initial PCR results should be
confirmed on samples drawn after a delay of a
month or more (3). At present, it seems that
although PCR is one of the most useful tests for
diagnosis of HIV infection in neonates and infants, it
is not definitive. A cautious reading of the situation
is that PCR should be interpreted with the aid of
careful follow-up examinations, preferably lasting
until the HIV antibody status of the infant is
resolved (3).

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Irinotecan provisionally released for
metastatic colon cancer

United States of America — The Food and Drug
Administration has granted accelerated release to
irinotecan (Camtozan®; Pharmacia/Upjohn) for the
treatment of metastatic colonic or rectal cancer that
has recurred or progressed after standard fluor-
ouracil-based chemotherapy.

Irinotecan is the first of a new class of antimetabo-
lites called camptothecins, which specifically inhibit
the cellular enzyme topoisomerase-I. In open phase
II studies infusion of the drug reduced tumour size
in 39 of 304 patients for an average duration of six
months. Unwanted effects included leukopenia and diarrhoea — which was sometimes prolonged and severe and, in some cases, required supportive medical treatment.

The FDA notes, in taking this decision, that colorectal cancer is diagnosed in 134,000 people in the United States each year, and that in 50% of these patients the disease recurs after primary treatment with surgery, adjuvant chemotherapy or radiotherapy. At present, there is little that can be offered to help these patients.

This decision has been taken on the advice of FDA’s Oncology Drugs Advisory Committee, which has provided advice on additional studies that should be conducted to evaluate further the safety and effectiveness of irinotecan.


Vasopressin for enuresis: danger of hyponatraemic convulsions

United Kingdom — The Committee on Safety of Medicines has advised that, since 1987, it has received 24 reports of hyponatraemic convulsions among patients (21 children and 3 adults) using an intranasal spray of vasopressin to control primary nocturnal enuresis (1).

Since symptomatic hyponatraemia can have dangerous consequences (2), the Committee emphasizes the need to take effective preventive measures, which should include:

• avoiding taking tricyclic antidepressants and other drugs which may increase the secretion of endogenous vasopressin;
• keeping to the recommended starting dose of 10 micrograms vasopressin in each nostril;
• warning patients to avoid excessive fluid intake;
• stopping treatment temporarily during illnesses that cause vomiting or diarrhoea to allow restitution of normal fluid and electrolyte balance.

References


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 (1-65) and Recommended (1-31) International Nonproprietary Names can be found in Cumulative List No. 8, 1992. 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 (1-65) et recommandées (1-31) dans la Liste récapitulative No. 8, 1992. 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 formuler de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations ne figurent pas dans les listes récapitulatives de DCI.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

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

Las listas de Denominaciones Comunes Internacionales Propuestas (1-65) y Recomendadas (1-31) se encuentran reunidas en Cumulative List No. 8, 1992. 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, estos datos descriptivos no deben incluirse en las listas recapitulatives de DCI.
Proposed International Nonproprietary Names: List 75
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 75 Proposed INN not later than 31 January 1997.

Dénominations communes internationales proposées: Liste 75
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 75 de DCI Proposées le 31 janvier 1997 au plus tard.

Denominaciones Comunes Internacionales Propuestas: Lista 75
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 75 de DCI Propuestas el 31 de enero de 1997 a más tardar.

<table>
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<td>Melatonin analogue</td>
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<td>agomelatina</td>
<td>(C_{15}H_{17}NO_{2})</td>
<td>138112-76-2</td>
</tr>
</tbody>
</table>

\(\text{C}_6\text{H}_3\text{N} - \text{OCH}_3\)
alatrofloxacinum
alatrofloxacin

7-[(1R,5S,6s)-6-[(S)-2-[(S)-2-aminopropionamido]propionamido]-3-azabicyc[3.1.0]hex-3-yl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1.8-naphthyridine-3-carboxylic acid
antibacterial

alatrofloxacine

Acide 7-[(1R,5S,6s)-6-[(2S)-2-[(2S)-2-aminopropionyl]amino]propionyl]-3-azabicyc[3.1.0]hex-3-yl]-1-(2,4-difluorophényl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylique
antibactérien

alatrofloxacino

ácido 7-[(1R,5S,6s)-6-[(S)-2-[(S)-2-aminopropionamido]propionamido]-3-azabiciclo[3.1.0]hex-3-yl]-1-(2,4-difluorofenil)-6-fluoro-1,4-dihidró-4-oxo-1,8-naftiridina-3-carboxílico
antibacteriano

C_{26}H_{25}F_{3}N_{6}O_{5} 157182-32-6

anseculinum
anseculin

7-methoxy-6-[[4-[o-methoxyphenyl]-1-piperazinyl]propoxy]-3,4-dimethylvonamn
nootropic agent

ansécultine

7-méthoxy-6-[[4-[2-méthoxyphényl]píparaizin-1-yl]propoxy]-3,4-diméthyl-2H-chromén-2-one
nootrope

anseculina

7-metoxi-6-[[4-[o-metoxifenil]-1-piperazínil]propoxi]-3,4-dimetilcumarina
nootrope

C_{26}H_{32}N_{2}O_{5} 155773-59-4
**aripiprazolum**
aripiprazole
7-[[4-[[2,3-dichlorophenyl]-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril antipsychotic

**aripiprazol**
aripiprazole
7-[[4-[[2,3-dichlorophényl]pipérazin-1-y]butoxy]-3,4-dihydroquinoléin-2(1H)-one antipsychotique

**aripiprazol**
aripiprazol
7-[[4-[[2,3-diclorofenil]-1-piperazinil]butoxi]-3,4-dihidrocarbostiril antipsicótico

C$_{23}$H$_{27}$Cl$_2$N$_3$O$_2$ 129722-12-9

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**arofyllinum**
arofylline
3-(p-chlorophenyl)-1-propylxanthine antiasthmatic

**arofylline**
3-(4-chlorophényl)-1-propyl-3,7-dihydro-1H-purine-2,6-dione antiasthmaticque

**arofilina**
3-(p-clorofenil)-1-propilxantina antiasmático

C$_{14}$H$_{13}$ClIN$_4$O$_2$ 136145-07-8

---

**atiprimodum**
atiprimod
2-[3-(diethylamino)propyl]-8,8-dipropyl-2-azaspiro[4.5]decano immunomodulator

**atiprimod**
3-[8,8-dipropyl-2 azaspiro[4.5]déc-2-yl]-N,N-diéthylpropan-1-amine immunomodulateur

**atiprimod**
2-[3-(dietilamino)propil]-8,9-dipropil-2-azaspiro[4.5]decano immunomodulador
beclomethasone
beclomethasone
beclomethasone
123018-47-3

immunoglobulin G 2a (mouse monoclonal IMMU-LL2 Fab' fragment γ-chain anti-human antigen CD 22), disulfide with mouse monoclonal IMMU-LL2 light chain
diagnostic agent

beclomethasone
beclomethasone
beclomethasone
159316-63-3

immunoglobulin G 2a (chaîne γ du fragment Fab' de l'anticorps monoclonal de souris IMMU-LL2 anti-antigène CD 22 humain), disulfure avec la chaîne légère de l'anticorps monoclonal de souris IMMU-LL2
produit à usage diagnostique

beclomethasone
beclomethasone
beclomethasone

immunoglobulina G 2a (cadena γ del fragmento Fab' del anticuerpo monoclonal de ratón IMMU-LL2 anti-antígeno CD 22 humano), disulfuro con la cadena ligera del anticuerpo monoclonal de ratón IMMU-LL2
agente de diagnóstico

beloxepinum
beloxepin
beloxepin
[α]-cis-1,3,4,13b-tetrahydro-2,10-dimethyl dibenz[2,3;6,7]oxepino^4,5-c^pyridin-4a(2H)-ol
antidepressant

beloxépine
beloxépine
beloxépine
(4a RS,13b RS)-2,10-dimethyl-1,3,4,13b-tétrahydro dibenzo[2,3;6,7]oxépino^4,5-c^pyridin-4a(2H)-ol
antidépresseur

beloxepina
beloxepina
beloxepina
(α)-cis-1,3,4,13b-tetrahdro-2,10-dimetildibenz[2,3;6,7]oxepino=4,5-c[d]piridin-4a(2H)-ol
antidepresivo

C19H21NO2
135028-30-2
**Bemiparinum natricum**

**Bemiparin sodium**

Sodium salt of depolymerized heparin obtained by alkaline degradation of quaternary ammonium salt of heparin from pork intestinal mucosa; the majority of the components have a 2-O-sulfo-4-enepyranosuronic acid structure at the non-reducing end and a 2-N,6-O-disulfo-D-glucosamine structure at the reducing end of their chain; the average relative molecular mass is about 3600 (3000 to 4200); the degree of sulfatation is about 2 per disaccharide unit.

**Bémiparine sodique**

Sel de sodium d'héparine dépolymérisée obtenue par fragmentation alcaline d'un sel d'ammonium quaternaire d'héparine de muqueuse intestinale de porc. La majorité des composants présentent une structure acide 2-O-sulfo-4-énepyranosuronique à l'extrémité non réductrice et une structure 2-N,6-O-disulfo-D-glucosamine à l'extrémité réductrice de leur chaîne. La masse moléculaire relative moyenne est voisine de 3600 (3000 à 4200). Le degré de sulfatation est voisin de 2 par unité disaccharide.

**Bemiparina sódica**

Sal de sodio de heparina despolimerizada obtenida por fragmentación alcalina de una sal de amonio cuaternario de heparina de mucosa intestinal de cerdo. La mayoría de los componentes presentan una estructura ácido 2-O-sulfo-4-enopiranosuránico en el extremo no reductor y una estructura 2-N,6-O-disulfo-D-glucosamina en el extremo reductor de su cadena. La masa molecular relativa media es aproximadamente 3600 (de 3000 a 4200). El grado de sulfatación es aproximadamente 2 por unidad de disacárido.

**Camadotinum**

**Cemadolin**

\(N,N\text{-dimethyl-L-valyl-L-valyl}-N\text{-methyl-L-valyl-L-prolyl-N-benzyl-L-prolinamide}\)

**Antineoplastic**

**Cemadotine**

\((N,N\text{-diméthyl-L-valyl})\text{-L-valyl-(N-méthyl-L-valyl-L-prolyl-(N-benzyl-L-prolinamide)}}\)

**Antinéoplasique**

**Cemadotina**

\(N,N\text{-dimetil-L-valile-L-valile-N-metil-L-valile-L-proile-N-bencil-L-prolinamida}\)

**Antineoplásico**

\(C_{35}H_{56}N_{6}O_{5}\)

159776-69-9
choriogonadotropinum alfa
choriogonadotropin alfa
human chorionic gonadotropin, glycoform α
α-subunit:
chorionic gonadotropin (human α-subunit protein moiety reduced)
β-subunit:
chorionic gonadotropin (human β-subunit protein moiety reduced)
*hormone*

choriogonadotropine alfa
gonadotropine chorionique humaine, forme glycoylée α
sous-unité α:
gonadotropine chorionique (partie protéique réduite de la sous-unité α humaine)
sous-unité β:
gonadotropine chorionique (partie protéique réduite de la sous-unité β humaine)
*hormone*

conogonadotropina alfa
gonadotropina coriónica humana, glicofoma α
subunidad α:
gonadotropina coriónica (fracción proteica reducida de la subunidad α humana)
subunidad β:
gonadotropina coriónica (fracción proteica reducida de la subunidad β humana)
*hormona*

α: C_{437}H_{188}N_{116}O_{134}S_{13} 58832-30-5
β: C_{366}H_{180}N_{116}O_{110}S_{13} 58832-34-9

177073-44-6

APDVQDCPEC TLQENPFPSP PGAPILQCMG CCFSSAYPTP
LRSSKTMILVQ KVNTSESTCC VAKSYNRTV MCGFVKVENHT
ACHCSTCYYH KS
SKEPLRPRKR FINATDAVEK EGCPCVCTVN TTTICAGYOPT
MTRVLQGVLP ALPQWVCNRY DVFESIRLP GCPGRVNPVF
SYAVASOCQC ALCRSSITDC GEPHDQPLTD EDPFRQDSSS
SKAPPPLPS FSELPGLDSPT PILPQ

clevidipinum
clevidipine
(±)-4-hydroxymethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, butylate (ester)
calcium channel blocker

clévidipine
(4R)-4-(2,3-dichlorophényl)-2,6-diméthyl-1,4-dihydropyridine-3,6-dicarboxylate de butanoyloxyméthyle et de méthyle
antagoniste calcique

clevadipino
(±)-4-(2,3-diclorofenil)-1,4-dihidro-2,6-dimetil-3,5-piridinadicarboxilato de butiriloximetilo y metilo
antagonista del calcio
deltibantum
deltibant
c-arginyl-L-arginyl-L-prolyl-trans-4-hydroxy-L-prolyl-glycyl-L-phenylalanyl-
L-cysteinyl-L-phenylalanyl-L-leucyl-L-arginine, 7,7'-bis(sulfide) with
(2R,2'S)-N,N'-hexamethylenbis[2-mercaptosuccinimide]
bradykinin receptor antagonist

\[ \text{C}_{128}\text{H}_{194}\text{N}_{40}\text{O}_{28}\text{S}_{2} \quad 140661-97-8 \]

\[ \text{D-Arg-Arg-Pro-Hyp-Gly-Phe-Cys-D-Phe-Leu-Arg} \]

\[ \text{D-Arg-Arg-Pro-Hyp-Gly-Phe-Cys-D-Phe-Leu-Arg} \]

donepezilum
donepezil
(±)-2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone
nootropic agent

donepézil
(2RS)-2-[(1-benzyl-4-piperidin-4-yl)méthyl]-5,6-diméthoxy-2,3-dihydro-1H-indén-
1-one
nootrope

donepezilo
(±)-2-[(1-bencil-4-pipendilmetyli]-5,6-dimetoxi-1-indanona
nootrope
dronedaronum

N-[2-butyl-3-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide

antianginal, antiarrhythmic

dronédarone

N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran-5-yl]methanesulfonamide

antiangoraux, antiarythmique

dronedarona

N-[2-butyl-3-[p-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]methanesulfonamide

antianginoso, antiarrítmico

C_{24}H_{29}NO_{3} 120014-06-4

ecamsulum

(±)-(3E,3'E)-3,3'-[p-phenylenedimethylidyne]bis[2-oxo-10-bornanesulfonic acid]

sunscreen

eçamsule

Acide [[1,4-Phénylénediméthylidyne]bis[(3E,3'E)-7,7-diméthyl-2-oxobicyclo[2.2.1]heptan-3-1-diy]] diméthanesulfonique

ecran solaire

eçaméul

(±)-(3E,3'E)-9,9'-[p-phenancemetilídino]bis[ácido 2-oxo-10-bornanosulfónico]

tint solar

C_{31}H_{44}N_{2}O_{5}S 141626-36-0
**efepristinum**

**efepristin**


**éfépristina**


**efepristina**


\[C_{44}H_{52}N_{8}O_{10}\] 57206-54-9

**elinafídum**

**elinafide**

\[N,N\'-\{triméthyleténbis(éthylénimino)\}dinaftalimide\] antineoplastic

**élinafide**

\[2,2\'-\{propane-1,3-diylbis(éthylénimino)\}bis[1H-benz[de]isoquinoléine-1,3(2H)-dione]\] antinéoplasique

**elinafida**

\[N,N\'-\{trimetilenobis(irninoetileno)\}dinaftalimida\] antineoplásico

\[C_{31}H_{26}N_{4}O_{4}\] 162706-37-8
filaminastum
filaminast
3'-cyclopentyloxy)-4'-methoxyacetophenone (E)-O-carbamoyloxime
antiasthmatic

filaminast
1-[3-(cyclopentyloxy)-4'-methoxyphenyl]éthanone (E)-O-carbamoyloxime
antiasthmatique

filaminast
3'-(cyclopentiloxi)-4'-metoxiacetofenona (E)-O-carbamoiloxima
antiasmático

C_{15}H_{20}N_2O_4
141184-34-1

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\text{O} \\
\text{N} \\
\text{O} \\
\text{NH}_2
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fibanserinum
fibansenn
1-[2-[4-\{(\alpha,\alpha,\alpha\text{-}trifluoro-\text{m-tolyl})\text{-}1\text{-}piperazinyl\}\text{ethyl}]\text{-}2\text{-}benzimidazolinone
antidepressant

fibansénne
1-[2-[4-[3-(trifluorométhyl])phényl]pipérazin-1-y[léthyl]-1,3-dihydro-2H-benzimidazol-2-one
antidépresseur

fibansenna
1-[2-[4-\{(\alpha,\alpha,\alpha\text{-}trifluoro-\text{n-tolyl})\text{-}1\text{-}piperazinyl\}\text{ethyl}]\text{-}2\text{-}benzimidazolinone
antidepresivo

C_{20}H_{21}F_3N_4O
167933-07-5

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\begin{array}{c}
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\text{N} \\
\text{N} \\
\text{N} \\
\text{NH}
\end{array}
\]

follitropinum beta
follitropin beta
follitropine bêta
hormone folliculo-stimulante, forme glycosylée β

\[
\text{follicle-stimulating hormone, glycoform } \beta \\
\alpha\text{-}subunit: \\
\text{chorionic gonadotropin (human } \alpha\text{-}subunit protein moiety reduced) \\
\beta\text{-}subunit: \\
\text{follicle-stimulating hormone (human } \beta\text{-}subunit protein moiety reduced) \\
\text{hormone}
\]

hormone folliculo-stimulante, forme glycosylée β

\[
\text{hormone folliculo-stimulante, forme glycosylée } \beta \\
\text{sub-unit } \alpha: \\
\text{gonadotropine chorionique (partie protéique réduite de la sous-unité } \alpha \text{ humaine) } \\
\text{sub-unit } \beta: \\
\text{hormone folliculo-stimulante (partie protéique réduite de la sous-unité } \beta \text{ humaine) } \\
\text{hormone}
\]
follitropina beta

hormona estimulante del folículo, glicoforma β
subunidad α:
gonadotropina coriónica (fracción proteica reducida de la subunidad α humana)
subunidad β:
hormona estimulante del folículo (fracción proteica reducida de la subunidad β)
foropantum
foropant
N,N-diméthyl-N'[(pyridin-3-y|méthyl)-N'-[2,4,6-tris(1-méthyléthyl)-phényl]thiazol-2-y|léthane-1,2-diamine
antagoniste du facteur activant les plaquettes
C_{28}H_{40}N_{4}S \quad 136463-36-5

icopezilum
icopezil
3-[2-(1-benzyl-4-pipendyl)ethyl]-5,7-dihydro-6H-pyrrolo[3,2-f]-1,2-benzisoxazol-6-one
nootropic agent
C_{23}H_{25}N_{3}O_{2} \quad 145508-78-7
Iofiupanum ([123I])

methyl 8-(3-fluoropropyl)-3β-(p-iodo-[123I]-phenyl)-1αH,5αH-nortropane-2β-carboxylate

diagnostic agent

Iofiupane ([123I])

(1R,2S,3S,5S)-8-(3-fluoropropyl)-3-[4-iodophenyl]-8-azabicyclo[3.2.1]octane-2-carboxylate de méthyle
produit à usage diagnostique

Iofiupano ([123I])

8-(3-fluoropropyl)-3β-(p-iodo-[123I]-fenil)-1αH,5αH-nortropane-2β-carboxilato de metilo
agente de diagnóstico

C_{18}H_{23}F_{123}INO_{2} \quad \text{155798-07-5}

Ivabradinum

3-[3-[[[7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl]methylamino]propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one
bradycardic agent

Ivabradine

3-[3-[[[7S)-3,4-diméthoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]méthyl]methylamino]propyl]-7,8-diméthoxy-1,3,4,5-tétrahydro-2H-3-benzazépin-2-one
bradicardisant

Ivabradina

3-[3-[[[7S)-3,4-dimetoxibiciclo[4.2.0]octa-1,3,5-trien-7-il]metil]metilamino]-propil]-1,3,4,5-tetrahidro-7,8-dimetoxi-2H-3-benzazepin-2-ona
bradicardizante

C_{27}H_{36}N_{2}O_{5} \quad \text{155974-00-8}
lagatidum
lagatide
lagatide
lagatida
L-prolyl-L-valyl-L-threonyl-L-lysyl-L-prolyl-L-glutaminyl-D-alaninamide
antidiarrhoeal
L-prolyl-L-valyl-L-threonyl-L-lysyl-L-prolyl-L-glutaminyl-D-alaninamide
antidiarrhéique
L-prolyl-L-valyl-L-threonyl-L-lysyl-L-prolyl-L-glutaminyl-D-alaninamide
antidiarreico
C_{33}H_{58}N_{10}O_{9}
157476-77-2
H-Pro—Val—Thr—Lys—Pro—Gln—D-Ala—NH₂

landiololum
landiolol
(-)-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl p-[(S)-2-hydroxy-3-[2-(4-morpholinecarboxamido)ethyl]amino]propanoate hydrocinnamate
beta-adrenoceptor antagonist
(-)-3-[4-[(2S)-2-hydroxy-3-[[2-(4-morpholin-4-ylcarbonyl)amino]éthyl]amino]propoxy]phénylpropanoate de [(S)-2,2-diméthyl-1,3-dioxolan-4-yl]méthyle
antagoniste beta-adrénérégalique
(-)-3-[4-[(2S)-2-hydroxy-3-[[2-(4-morpholin-4-ylcarboxamido)éthyl]amino]propoxy]propanoate de [(S)-2,2-diméthyl-1,3-dioxolan-4-yl]méthyle
antagonista de los receptores beta-adrenérgicos
C_{25}H_{39}N_{3}O_{8}
133242-30-5

lefradafibanum
lefradafiban
(3S,5S)-5-[[4'-[carboxyamidino]-4-biphenyl]oxy]methyl]-2-oxo-3-pyrrolidineacetic acid, dimethyl ester
fibrinogen receptor antagonist
(3S,5S)-5-[[4'-[imino[(méthoxycarbonyl)amino]méthyl]-biphenyl-4-y]oxy]méthyl]-2-oxopyrrolidin-3-ylacétate de méthyle
antagoniste du récepteur du fibrinogène
éster dimetílico del ácido(3S,5S)-5-[[4'-carboxiamidino]-4-bifeniloxy]metil]-2-oxo-3-pirrolidinaético
antagonista de los receptores del fibrinógeno
C_{23}H_{25}N_{3}O_{6}
149503-79-7
marimastatum

(2S,3R)-3-[(1S)-2,2-dimethyl-1-(methylcarbamoyl)propyl]carbonyl]-2-hydroxy-5-methylhexanohydroxamic acid
antineoplastic

maxacalcitolum

(+-)-(5Z,7E)-20-[(3-hydroxy-3-methylbutoxy)-9,10-seco]pregna-5,7,10(19)-triene-1\(\alpha\),3\(\beta\)-diol
vitamin D analogue

maxacalcitolum

(+-)-(5Z,7E)-20-[(3-hydroxy-3-methylbutoxy)-9,10-seco]pregna-5,7,10(19)-triene-1\(\alpha\),3\(\beta\)-diol
analogue de la vitamine D

maxacalcitolum

(+-)-(5Z,7E)-20-[(3-hydroxy-3-methylbutoxy)-9,10-seco]pregna-5,7,10(19)-triene-1\(\alpha\),3\(\beta\)-diol
análogo de la vitamina D

C\(_{26}\)H\(_{42}\)O\(_{4}\) 103909-75-7
mazokalimum

mazokalim

ethyl 5-[(3S,4R)-4-[(1,6-dihydro-6-oxo-3-pyridazinyl)oxy]-3-hydroxy-2,2,3-trimethyl-6-chromanyl]-1H-tetrazole-1-butyrate

potassium channel activator

nifekalantum

nifekalant

6-[[2-(2-hydroxyethyl)[3-(p-nitrophenyl)propyl]amino]ethyl]amino]-1,3-dimethyluracil

potassium channel blocker

nifékélang

6-[[2-(2-hydroxyéthyl)[3-(4-nitrophényl)propyl]amino]éthyl]amino]-1,3-diméthylpyrimidin-2,4[H,3H]-dione

bloquant des canaux potassiques

nifekalant

6-[[2-(2-hidroxietil)[3-(p-nitrofenil)propil]amino]etil]amino]-1,3-dimetiluracilo

bloqueante de los canales de potasio

C$_{23}$H$_{28}$N$_6$O$_6$ 164173-54-5

C$_{13}$H$_{27}$N$_5$O$_5$ 130636-43-0
nolpitantil besilas
nolpitantium besilate
1-[2-[[S]-3-(3,4-dichlorophenyl)-1-[[m-isopropoxyphenyl]acetyl]-3-piperidyl]ethyl-4-phenylquinuclidium benzenesulfonate
tachykinin receptor antagonist

bésilate de nolpitantium
benzènesulfonate de 1-[2-[[S]-3-(3,4-dichlorophényl)-1-[[2-[[3-(1-méthyléthoxy)phényl]acétyl]pipéridin-3-y]léthy]-4-phenyl-1-azoniabicyclo[2.2.2]octane
antagoniste de récepteurs de la tachykinine

besilato de nolpitantio
benzenosulfonato de 1-[[2-[[S]-3-(3,4-diclorofenil)-1-[[m-isopropoxifenil]acetil]-3-piperidil]etil]-4-fenilquinuclidnio
antagonista de los receptores de taquiquinina

C_{43}H_{50}Cl_{2}N_{5}O_{5}S 155418-06-7

orbofibanum
orbofiban
N-[[3S]-1-{{p-amidinophenyl}-2-oxo-3-pyrrolidinyl}carbamoyl]-β-alanine, ethyl ester
fibrinogen receptor antagonist

orbofiban
3-[[3S]-1-{{4-carbamimidoylphényl}-2-oxopyrrolidin-3-y}lursido]propanoate d'éthyle
antagoniste du récepteur du fibrinogène

orcolibén
éster etílico de la N-[[3S]-1-{{p-amidinofenil}-2-oxo-3-prrolidindl}carbamoyl]-β-alanina
antagonista de los receptores del fibrinogena

C_{17}H_{23}N_{5}O_{4} 163250-90-6
**pranazepidum**

(-)-N-[(S)-1-(o-fluorophenyl)-3,4,6,7-tetrahydro-4-oxopyrrolo-[3,2,1-jk][1,4]benzodiazepin-3-yl]indole-2-carboxamide

*cholecystokinin receptor antagonist*

**pranazépide**

(-)-N-[(3S)-1-{2-fluorophényl)-4-oxo-3,4,6,7-tétrahydropyrrolo-[3,2,1-jk][1,4]benzodiazépin-3-yl]-1H-indole-2-carboxamide

*antagoniste du récepteur de la cholécystokinine*

**pranazepida**

(-)-N-[(S)-1-(o-fluorofenil)-3,4,6,7-tetrahidro-4-oxopïrrolo-[3,2,1-jk][1,4]benzodiazepin-3-il]índol-2-carboxam¡da

*antagonista de los receptores de la colecistoquinina*


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**rizatriptanum**

(rizatriptan)

3-[2-(dimethylamino)ethyl]-5-[(1H-1,2,4-triazol-1-yl)methyl]indole

*antimigraine, serotonin receptor agonist*

**rztatriptan**

N,N-diméthyl-2-[5-[(1H-1,2,4-triazol-1-yl)méthyl]-1H-indol-3-yl]éthanamine

*antimigraineux, agoniste de la sérotonine*

**rztatriptán**

3-[2-(dimetilamino)etil]-5-[(1H-1,2,4-tríazol-1-ilmeti])indol

*antimigráñoso, agonista de los receptores de la serotonina*


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*WHO Drug Information, Vol. 10, No 2, 1996*
saredutantum
saredutant

N-[(S)-p-[2-(4-acetamido-4-phenylpiperidino)ethyl]-3,4-dichlorophenethyl]-
N-methylbenzamide

tachykinin receptor antagonist

saredutant

N-[(2S)-4-[4-(acétylamino)-4-phénylpipéridin-1-yl]-2-(3,4-
dichlorophényl)butyl]-N-méthylbenzamide

antagoniste de récepteurs de la tachykinine

saredutant

N-[(S)-p-[2-(4-acetamido-4-fenilpiperidino)etil]-3,4-diclorofenetil]-
N-metilbenzamida

antagonista de los receptores de taquiquinina

C<sub>31</sub>H<sub>35</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub> 142001-63-6

sitafloxacinum
sitafloxacin

(-)-7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-8-chloro-6-fluoro-
1-{[1R,2S]-2-fluorocyclopropyl}-1,4-dihydro-4-oxo-3-quinolinicarboxylic acid
antibacterial

sitafloxacine

acide (-)-7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-8-chloro-6-fluoro-
1-{[1R,2S]-2-fluorocyclopropyl}-4-oxo-1,4-dihydroquinoléin-3-carboxylique
antibactérien

sitafloxacino

ácido (-)-7-[(7S)-7-amino-5-azaspiro[2.4]hept-5-yl]-8-cloro-6-fluoro-
1-{[1R,2S]-2-fluorociclopropil}-1,4-dihidro-4-oxo-3-quinolinaaceticico
antibacteriano

C<sub>19</sub>H<sub>18</sub>CIF<sub>2</sub>N<sub>3</sub>O<sub>3</sub> 127254-12-0
**sulesomab**
sulesomab

immunoglobulin G 1 (mouse monoclonal IMMU-MN3 Fab' fragment γ-chain anti-human NCA-90 granulocyte cell antigen), disulfide with mouse monoclonal IMMU-MN3 light chain
diagnostic agent

**sulésomab**
sulésomab

immunoglobuline G 1 (chaîne γ du fragment Fab' de l'anticorps monoclonal de souris IMMU-MN3 anti-antigène de granulocyte humain NCA-90), disulfure avec la chaîne légère de l'anticorps monoclonal de souris IMMU-MN3
produit à usage diagnostique

**sulesomab**
sulesomab

immunoglobulina G 1 (cadena γ del fragmento Fab' del anticuerpo monoclonal de ratón IMMU-MN3 anti-antígeno de granulocito humano NCA-90), disulfuro con la cadena ligera del anticuerpo monoclonal de ratón IMMU-MN3
agente de diagnóstico

167747-19-5

taltirelinum
taltirelin

(-)-N-[(S)-hexahydro-1-methyl-2,6-dioxo-4-pyrimidinyl]carbonyl-L-histidyl-L-prolinamide
thyrotropin releasing hormone (TRH) analog

taltiréline
taltiréline

(-)-(2S)-1-[(2S)-3-(1H-imidaizol-4-yl)-2-[[[(4S)-1-méthyl-2,6-dioxohexahydro-pyrimidin-4-yl]carbonyl]amino]propanoyl]pyrrolidine-2-carboxamide
 analogue de l'hormone de libération de la thyrotrophine

taltiragina
taltiragina

(-)-N-[(S)-hexahydro-1-metil-2,6-dioxo-4-pirimidinil]carbonil-L-histidil-L-prolinamida
analogó de la hormona liberadora de tirotropina

C_{17}H_{23}N_{7}O_{5} 103300-74-9

![Chemical Structure](attachment:structure.png)

**talviralinum**
talviraline

isopropyl [2S]-3,4-dihydro-7-methoxy-2-[(methylthio)methyl]-3-thioxo-1(2H)-quinoxalinecarboxylate
antiviral

talviraline

(2S)-7-méthoxy-2-[(méthylsuifanyl)méthyl]-3-thioxo-3,4-dihydroquinoxaline-1(2H)-carboxylate de 1-méthyléthyle
antiviral

talviralina

(2S)-3,4-dihidro-7-metoxi-2 [metilbromo]métihl]-3-thixo-1[2H]-quinoxalinecarboxilato de 1-metilétile
antiviral
technetium ($^{99m}$Tc) pintumomab

Immunoglobulin G 1 (mouse monoclonal 170 γ-chain anti-human adenocarcinoma antigen), disulfide with mouse monoclonal 170 κ-chain, dimer, [$^{99m}$Tc]technetium salt radiodiagnostic agent

techn étium ($^{99m}$Tc) pintumomab

Sal de [$^{99m}$Tc]technétium de l'immunoglobuline G 1 (chaîne γ de l'anticorps monoclonal de souris 170 anti-antigène associé à l'adénocarcinome humain), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris 170 produit à usage radiodiagnostique

technetium ($^{99m}$Tc) pintumomab

Sal de [$^{99m}$Tc]technetium del inmunoglobulina G 1 (cadena γ del anticuerpo monoclonal de ratón 170 anti-antígeno asociado al adenocarcinoma humano), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón 170 agente de radiodiagnóstico

terbogrelum

(5E)-6-[m-(3-tert-butyl-2-cyanoguanidino)phenyl]-6-(3-pyridyl)-5-hexenoic acid platelet aggregation inhibitor

terbogrel

ácido (5E)-6-[m-(3-terc-butil-2-cianoguanidino)fenil]-6-(pirid-3-yl)hex-5-énico inhibidor de la agregación plaquetaria

terbogrel

ácido (5E)-6-[m-(3-tert-butyl-2-cyanoguanidino)fenil]-6-(3-piridil)-5-hexenóico inhibidor de la agregación plaquetaria

C$_{23}$H$_{27}$N$_{5}$O$_{2}$ 149979-74-8
tresperimusum
tresperimus
[4-(3-aminopropyl)amino]butyl]carbamic acid, ester with
N-(6-guanidinohexyl)glycolamide
** immnosuppressant

trespérimus
[4-(3-aminopropyl)amino]butyl]carbamate de 2-[(6-guanidinohexyl)amino]-
2-oxoéthyle
** immnosupresseur

tresperimus
[4-(3-aminopropyl)amino]butyl]carbamato de [(6-guanidinohexil)carbamoil]=
- métilo
immunosupresor

C_{17}H_{37}N_{7}O_{3} 160677-67-8

vinflurinum
vinflunine
4'-deoxy-20',20'-difluoro-8'-norvincaleukoblastine
** antineoplastic

vinflunine
20',20'-difluoro-4'-dèsoxy-8'-norvincaleucoblastine
** antineoplasique

vinflunina
4'-desoxi-20',20'-di(luoro-8'-norvincaleucoblastina
** antineoplásico

C_{45}H_{54}F_{2}N_{4}O_{8} 162652-95-1

\begin{center}
\includegraphics[width=\textwidth]{chemical_structures.png}
\end{center}

**AMENDMENTS TO PREVIOUS LISTS**

**Proposed International Nonproprietary Names (Prop. INN): List 62**

(*WHO Drug Information, Vol. 3, No. 4, 1989*)

p. 6  dosmalfatum  replace the chemical name and the molecular formula by the following:

[p-
[(diosmin heptasulfato](7-)]tetracocontahydroxytetradecaaluminium

C_{28}H_{43}Al_{14}O_{71}S_{7}
Proposed International Nonproprietary Names (Prop. INN): List 74
Dénominations communes internationales proposées (DCI Prop.): Liste 74
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 74

(WHO Drug Information, Vol. 9, No. 4, 1995)

p. 5
apadollinum
apadoline

replace the chemical name by the following:
(+)-10-[(1R)-methyl-2-(1-pyrrolidinyl)ethyl]-N-propylphenothiazine-2-carboxamide

apadolina

sustituyese el nombre químico por el siguiente:
(+)-10-[(1R)-metil-2-(1-pirrolidinil)etil]-N-propilfenotiazina-2-carboxamida

p. 6
asimadollinum
asimadoline

replace the chemical name by the following:
N-{(αS)-α-[[(3S)-3-hydroxy-1-pyrrolidinyl]methyl]benzyl}-N-methyl-2,2-diphenylacetamide

asimadolina

sustituyese el nombre químico por el siguiente:
N-{(αS)-α-[[(3S)-3-hidroxi-1-pirrolidinil]metil]bencil}-N-metil-2,2-difenilacetamida

p. 6
atliprofenum
atliprofen
atliprofène
atliprofeno

add the following CAS registry number:

asimadolinum

insérer le numéro dans le registre du CAS suivant:

insérése el siguiente número de registro del CAS:

156686-09-7

p. 9
dabelotinum
dabelotine

dabelotina

remplacer le nom chimique par:

(±)-1-méthyl-B-[[(2RS)-morpholin-2-yl]méthoxy]-1,2,3,4-tétrahydroquinoléine

p. 14
fexofenadinum
fexofenadine
fexofénadine
fexofenadina

replace the CAS registry number by the following:

remplacer le numéro dans le registre du CAS par:

sustituyase el número de registro del CAS por el siguiente:

83799-24-0

p. 21
milodistimum
milodistim
milodistim
milodistim

replace the graphic formula by the following:

remplacer la formule développée par:

sustituyase la fórmula desarrollada por la siguiente:

APARSPSPT QPWEHVAIQQ EALRLDDLRSX DTAAEMNVEV
KEVISEFDELQ EPTCLQURLIE LYTGQLRGLSL TKLKGPLTHN
ASNykQKCP PPPETSCATQI ITFESFKENL KDFLLVIPFD
CWEFVQEGGG SSGGGGGGASP MTQTTPFLKTS WYDCSNMIDR
IITHLQCPPPL PLLDFNINLG EDQQLMRNIN LRRPNLEAPN
RAVKSILQDAS AIESILKNNLL PCLPLATAAP TRDIPIHICDG
DNNEPRRRLT FYKTLLENAQ AQQTTTLSLAT F
p. 22 osanetantum

osanant

replace the chemical name and the graphic formula by the following:

\[N\{1\{[3\{[\{\text{H}\}-1\text{-benzoyl-3\{3,4\text{-dichlorophenyl}-3\text{-piperidyl}\text{propyl}]4\text{-phenyl-4-piperidyl}\text{-N-methylacetamide}}\]}}\]

p. 23 pagoclonum

pagoclone

replace the graphic formula by the following:

\[
\text{remplacer la formule développée par:}
\]

p. 29 samarii (153Sm) lexidronanum

samarium (153Sm) lexidron

remplacer le nom chimique par:

\[
\text{pentahydrogéno (OC-6-21)-[éthylénebis(nitrilodiméthylène)]= tétraphosphonato\{8\}-N,N',O',O',O,O',O',O'}\text{smarate(5-)}\] ^\text{153Sm}
\]

p. 30 sildenafilum

sildenafil

remplacer le nom chimique par:

\[
1\{[4\{5\text{-thoxy-3-}[1\{méthyl-7-oxo-3\text{-propyl]-6,7\text{-ciydro-1-f-}
\text{pyrazoloc[4,3-d]pyrimidin-5-yl]phényl}2\text{ulfonyl]-4-méthylpipérazine}}\]
\]
p.33 xemilofibanum
xemilofiban
xémilofiban
xemilofiban
replace the CAS registry number by the following:
remplacer le numéro dans le registre du CAS par:
sustituyase el número de registro del CAS por el siguiente:
149820-74-6

p.33 zinostatinum stimalamerum
zinostatin stimalamer
zinostatine stimalamère
zinostatina estimalámero
replace the description by the following:
replace the description by the following:
replace the description chimique par:
la description chimique par:
la descripción por el siguiente:
substance produced by combining two parts of styrene-alt-maleic acid
copolymer that is partially butyl esterized with one part of zinostatin
substance obtenue par combinaison de deux parties d'un copolymère alterné
de styrène et d'acide maléique partiellement estérifié par de l'alcool butylique
avec une partie de zinostatine (néocarzinostatine)
sustancia producida por combinación de una parte de zinostatina y los
partes de copolímero de estireno-alt-ácido maléico parcialmente esterificado
con butilo

MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES

Dénominations communes internationales proposées (DCI Prop.): Liste 62
(Informations pharmaceutiques OMS, Vol. 3, No. 4, 1989)

p. 5 dosmalfatum
dosmalfate
remplacer le nom chimique et la formule brute par:
[y₇-[(diosmin heptasulfato)(7-)]téracontahydroxytétradécaaluminium
C₂₈H₆₀Al₁₄O₇₁S₇
Pour toutes modifications apportées aux Dénominations communes internationales proposées (DCI Prop.): Listes 71-74 voir page 112, section AMENDMENTS TO PREVIOUS LISTS.

MODIFICACIONES A LAS LISTAS ANTERIORES

Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Liste 62
(Información Farmacéutica, OMS, Vol. 4, No. 4, 1989)

p. 5 dosmalfatum
dosmalfato
sustituyase el nombre químico y la fórmula empírica por los siguientes:
[y₇-[(diosmin heptasulfato)(7-)]téracontahidroxitétradécaaluminio
C₂₈H₆₀Al₁₄O₇₁S₇
Para cualquier modificación de las Denominaciones Comunes Internacionales Propuestas (DCI Prop.):
Listas 71-74 vease página 112, sección AMENDMENTS TO PREVIOUS LISTS.
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 Organization1 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.

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.

A. Such objection shall:

(i) identify the person objecting;

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1 Text adopted by the Executive Board of WHO in resolution EB15.R7 (Off. Rec. Wid Health Org., 1955, 60, 3) and amended by the Board in resolution EB43.R9 (Off. Rec. Wid 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 “y” instead of “v”; 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. Where a stem is shown without any hyphens it may be used anywhere in the name.

<table>
<thead>
<tr>
<th>Latin</th>
<th>English</th>
</tr>
</thead>
<tbody>
<tr>
<td>-acum</td>
<td>anti-inflammatory agents of the ibufenac group</td>
</tr>
<tr>
<td>-actidum</td>
<td>synthetic polypeptides with a corticotropin-like action</td>
</tr>
<tr>
<td>-adol</td>
<td>analgesics</td>
</tr>
<tr>
<td>-astum</td>
<td>antiasthmatic, antiallergic substances not acting primarily as antihistaminics</td>
</tr>
<tr>
<td>-astine</td>
<td>antihistaminics</td>
</tr>
<tr>
<td>-azepamum</td>
<td>diazepam derivatives</td>
</tr>
<tr>
<td>-bactamum</td>
<td>β-lactamase inhibitors</td>
</tr>
<tr>
<td>-bol</td>
<td>steroids, anabolic</td>
</tr>
<tr>
<td>-buzone</td>
<td>anti-inflammatory analgesics, phenylbutazone derivatives</td>
</tr>
<tr>
<td>-caine</td>
<td>antifibrillant substances with local anaesthetic activity</td>
</tr>
<tr>
<td>-calma</td>
<td>local anaesthetics</td>
</tr>
<tr>
<td>-cef</td>
<td>antibiotics, cefalosporanic acid derivatives</td>
</tr>
<tr>
<td>-cellum</td>
<td>antibiotics, derivatives of β-aminopenicillin acid</td>
</tr>
<tr>
<td>-conazolum</td>
<td>systemic antifungal agents, miconazole derivatives</td>
</tr>
<tr>
<td>-cort</td>
<td>corticosteroids, except prednisolone derivatives</td>
</tr>
<tr>
<td>-dipinum</td>
<td>calcium channel blockers, nifedipine derivatives</td>
</tr>
<tr>
<td>-fibratum</td>
<td>clofibrate derivatives</td>
</tr>
<tr>
<td>-gast</td>
<td>steroids, progestogens</td>
</tr>
<tr>
<td>-gl-</td>
<td>sulfonamide hypoglycaemics</td>
</tr>
<tr>
<td>-i-</td>
<td>iodine-containing contrast media</td>
</tr>
<tr>
<td>-i-um</td>
<td>quaternary ammonium compounds</td>
</tr>
<tr>
<td>-metacinum</td>
<td>anti-inflammatory substances, indomethacin derivatives</td>
</tr>
<tr>
<td>-mycin</td>
<td>antibiotics, produced by Streptomyces strains</td>
</tr>
<tr>
<td>-nidazolum</td>
<td>antiprotozoal substances, metronidazole derivatives</td>
</tr>
<tr>
<td>-olol</td>
<td>β-adrenoceptor antagonists</td>
</tr>
<tr>
<td>-oxacinum</td>
<td>antibacterial agents, nalidixic acid derivatives</td>
</tr>
<tr>
<td>-pndum</td>
<td>sulpiride derivatives</td>
</tr>
<tr>
<td>-proliatatum</td>
<td>angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>-profenum</td>
<td>anti-inflammatory substances, ibuprofen derivatives</td>
</tr>
<tr>
<td>-prost</td>
<td>prostaglandins</td>
</tr>
<tr>
<td>-relin</td>
<td>hypothalamic hormone release-stimulating peptides</td>
</tr>
<tr>
<td>-tenolum</td>
<td>bronchodilators, phenethyline derivatives</td>
</tr>
<tr>
<td>-tidinum</td>
<td>histamine H1-receptor antagonists</td>
</tr>
<tr>
<td>-trexatum</td>
<td>folic acid antagonists</td>
</tr>
<tr>
<td>-verinium</td>
<td>spasmylytics with a papaverine-like action</td>
</tr>
<tr>
<td>-vin-</td>
<td>vinca alkaloids</td>
</tr>
</tbody>
</table>

1 A more extensive listing of stems is contained in the working document Pharm. S/Nom. 15 which is regularly updated and can be requested from Pharmaceuticals, WHO, Geneva.
Annexe 1

PROCEDURE A SUIVRE EN VUE DU CHOIX DE DENOMINATIONS COMMUNES INTERNATIONALES RECOMMANDÉES 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 et par l'envoi d'une lettre aux États Membres et aux commissions nationales de pharmacopée ou autres organismes désignés par les États 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 États 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 (voir l'article 3).


1 Depuis janvier 1955, 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 (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 issues 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 de 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 "f" 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.

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<td>-mycine</td>
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1 Une liste plus complète de segments clés est contenue dans le document de travail Pharm S/Nom 15 qui est régulièrement mis à jour et qui peut être demandé auprès de l'Unité pharmaceutique, OMS, Genève.
### Anexo 1

**PROCEDIMIENTO DE SELECCIÓN 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 Cuatro 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 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 envueltas también a las personas que tuvieron un interés especial en una denominación objeto de estudio.

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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 estude 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 conforma 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 ORIENTACIÓN PARA FORMAR DENOMINACIONES COMUNES INTERNACIONALES PARA SUSTANCIAS FARMACEUTICAS*

1. Las Denominaciones Comunes Internacionales (DCI) deberán diferenciarse tanto fonéticamente como ortográficamente. No deberán ser incomodamente 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 sugestiones 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 inactivas.

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 "l" 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. 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 originadas 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.

† El documento de trabajo Pharm S/Norm 15, que se pone al día regularmente, contiene una lista más extensa de partículas comunes. Las personas que deseen recibirlo deberán solicitar su envío al Servicio de Preparaciones Farmacéuticas, OMS, Ginebra (Suiza).
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