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PHARMACEUTICALS: RESTRICTIONS IN USE AND AVAILABILITY

April 2003

Essential Drugs and Medicines Policy
Quality Assurance and Safety: Medicines
Health Technology and Pharmaceuticals
World Health Organization

PHARMACEUTICALS:
RESTRICTIONS IN USE AND AVAILABILITY

Prepared within the context of the United Nations publication

"Consolidated List of Products whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments"

Update of the Sixth Issue - April 2003

Essential Drugs and Medicines Policy
Quality Assurance and Safety: Medicines
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This text is the third update to the Sixth Issue of the United Nations Consolidated List of Products whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments - Pharmaceuticals (UN General Assembly Resolutions 37/137, 1982; 38/149, 1983; 39/229, 1984; 44/226, 1989). It is offered as a service to drug regulators, the pharmaceutical industry, and to everyone interested in assuring the safe and rational use of drugs. It complements and consolidates other drug-related information issued by the World Health Organization, including the WHO Rapid Alerts, WHO Pharmaceuticals Newsletter and the quarterly subscription journal WHO Drug Information.

Scope and presentation

This volume presents information on new national regulatory decisions, and on voluntary withdrawal of products by manufacturers on grounds of safety, that were reported to WHO up to December 2002.

Products are listed alphabetically within sections; International Nonproprietary Names (INNs) have been used whenever possible. Each product entry includes, where available, the Chemical Abstracts Service registry number (CAS number); synonyms including other generic names and chemical names; the effective date on which the regulation came into force; a summary of regulatory measures taken by governments; brief explanatory comments where necessary; and legal and bibliographical references.

While the information cannot be regarded as exhaustive, either in terms of products or regulatory measures, it covers regulatory actions taken by a total of 27 governments on 56 products. It should be noted, none the less, that decisions taken by a limited number of governments on a specific product may not be representative of the positions of other governments. Moreover, the fact that a given product is not listed as regulated by a country does not necessarily mean that it is permitted in that country; it may mean that the relevant regulatory decision has not been communicated to WHO or that the product has not been submitted for registration. The efficacy of products listed is not addressed, but is an aspect that may be crucial when a government is considering regulatory action.

Criteria for the inclusion of products in the Consolidated List (see next page) were developed in 1985 and revised in the light of the comments received from governments. However, governments' interpretation of the criterion "severely restricted", in particular, continues to vary widely, leading to considerable unevenness in reporting. When necessary, additional information and/or clarification has been requested from governments; products which clearly do not meet the criteria have been omitted after consultation with governments. Information received from non-governmental organizations has, in each case, been verified with governments.

The information provided also includes references to relevant legal or statutory documents that enable the user to ascertain the legal context and scope of the regulations. Such references cannot be given for most entries relating to specific pharmaceutical products since the relevant licenses are often made or amended by an administrative decision which is not published. Brief explanatory comments also appear, where necessary, to clarify certain regulatory actions and put them into broader context.

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Alphabetical listing

Monocomponent products

Group products

Combination products

Product Name: Acetylsalicylic acid

CAS number: 50-78-2

Scientific and Common Names, Synonyms:

2-Acetoxybenzoic acid;

Aspirin

Country	Effective Date	Description of action taken Grounds for decision
Brazil	June 2001	The National Health Surveillance Agency requires all pharmaceutical products containing acetylsalicylic acid to bear a warning against using such products in children with chicken pox or flu symptoms without consulting a physician about Reye's syndrome (Reference: Resoluçao 529/ANVISA,06/08/2001. As communicated to WHO, 13 September 2001).
UK	October 2002	The Medicines Control Agency (MCA) has restricted the use of acetylsalicylic acid products in 16 year old and younger children since the risk of aspirin associated Reye's syndrome exists in all children up to this age group. All acetylsalicylic acid containing products are required to include this restriction in the product monograph (Reference: Medicines Control Agency Statement 2002/0436, 22 October 2002, available from URL: http://www.mca.gov.uk).

Product Name: Aristolochic acid

CAS number: 313-67-7

Scientific and Common Names, Synonyms:

8-Methoxy-3,4-methylenedioxy-10-nitro-1-phenanthrenecarboxylic acid;

Acidum aristolchicum

Country	Effective Date	Description of action taken Grounds for decision
Australia	December 2001	A traditional product named Longdan Qiegan Wan (Wetness Heat Pill) has been removed from the Australian Register of Therapeutic Goods since it contains aristolochic acid known to cause kidney damage and urinary tract cancer (Reference: Therapeutic Goods Administration Media Release, 7 December 2001. Available from URL: http://www.health.gov.au).
Canada	October 2001	Health Canada has issued a Customs Alert to prevent the sale and import of products containing aristolochic acid. Manufacturers, retailers and importers have been requested to withdraw from the market all existing products containing aristolochia and aristolochic acid (Reference: Health Canada Warnings / Advisories, 5 October

		2001; 24 August 2001; 16 May 2002. Available from URL: http://www.hc-sc.gc.ca).
France	July 2001	All homeopathic preparations containing *Aristolochia brasiliensis* and homeopathic preparations containing products belonging to *Aristolochiaceae* or related plant families have been withdrawn due to risks of nephrotoxicity and carcinogenicity associated with aristolochic acid (Reference: Communication to WHO, 5 October 2001).
Oman	July 2001	Prohibition of import and marketing in view of kidney toxicity and urinary tract cancer associated with aristolochic acid (Reference: Ministry of Health, Directorate of Pharmaceuticals Affairs and Drug Control Circular No. 25/2001. As communicated to WHO, 2 October 2001).
USA	April 2001	The FDA has cautioned consumers against consuming any dietary supplement or traditional medicine containing aristolochic acid (Reference: Media Release, 11 April 2001. Available from URL: http://www.hc-sc.gc.ca).

Product Name: Astemizole

CAS number: 68844-77-9

Scientific and Common Names, Synonyms:

1-(4-Fluorobenzyl)benzimidazol-2-yl[1-(4-methoxyphenethyl)-4-piperidyl] amine;

Astezol, Astol

Country	Effective Date	Description of action taken Grounds for decision
Brazil	June 2001	Registration cancelled due to several adverse reactions (Reference: Resoluçao n.526/ANVISA,06/08/2001. As communicated to WHO, 13 September 2001).

Product Name: Cerivastatin

CAS number: 145599-86-6

Scientific and Common Names, Synonyms:

(3R, 5S, 6E)-7-[4-(4-Fluorophenyl)-2,6-diisopropyl-5-(methoxymethyl)-3-pyridyl]-3,5-dihydroxy-6-heptenoic acid;

Cholstat, Lipobay, Rivastatin

Country	Effective Date	Description of action taken Grounds for decision
USA	November 1999	Prescribing information was changed to include a contraindication for the combined use of cerivastatin and gemfibrozil.

USA	May 2001	The Dosage and Administration section was revised to highlight that 0.4 mg is the starting dose for cerivastatin (Reference: 'Dear Healthcare Professional' letters from Bayer Pharmaceutical Division. Available from URL: http://www.fda.gov/medwatch).
Canada	March 2001	Prescribing information was changed to include a contraindication for the combined use of cerivastatin and gemfibrozil.
	July 2001	The prescribing information was revised to recommend a starting dose of 0.2 mg (Reference: 'Dear Healthcare Professional' letter from Bayer Pharmaceutical Division. Available from URL: http://www.hc-sc.gc.ca/).
Australia	February 2001	Prescribing information was changed to include a contraindication for the combined use of cerivastatin and gemfibrozil and warning issued to alert prescribers to the possibility of rhabdomyolysis with all statins.(Reference: Australia Adverse Drug Reactions Bulletin, Vol 20(1), February 2001).
Europe	June 2001	Europe-wide regulatory action was taken to reduce the risk of rhabdomyolysis, when the concomitant use of cerivastatin and gemfibrozil was contraindicated and the maximum daily dose of cerivastatin was reduced to 0.4 mg (Reference: Drug Safety Information from the Committee on Safety of Medicines, Medicines Control Agency, 8 August 2001. Available from URL: http://www.mca.gov.uk).
Worldwide	August 2001	Cerivastatin was voluntarily withdrawn from world market by the parent company (Bayer) on account of the increased risk of rhabdomyolysis associated with its use, particularly when used in combination with gemfibrozil.(Reference: FDA Talk Paper TOI-34, 8 August 2001. Available from URL: http://www.fda.gov).

Product Name: **Cisapride**

CAS number: **81098-60-4**

Scientific and Common Names, Synonyms:

cis-4-Amino-5-chloro-N-[1-[3-(p-fluorophenoxy)propyl]-3-methoxy-4-piperidyl]-*o*-anisamide;

Cismotil, Cisapid, Digenol

Country	Effective Date	Description of action taken Grounds for decision
Bahrain	May 2001	Cisapride was withdrawn from the local market in May 2001. The action was based on reports of serious cardiac events (Reference: Communication to WHO, 20 August 2001).
Brazil	April 2001	The National Health Surveillance Agency severely restricted the use of cisapride through prescription and suspended the marketing authorization with the exception of manufacturers with their own Pharmacovigilance System (Reference: Resoluçao n.530/ANVISA, 04/18/2001. As communicated to WHO, 13 September 2001).

Chile	July 2001	The Public Health Institute of Chile has restricted the indications for cisapride because of the risk of serious cardiac adverse effects. The use in children is contraindicated (Reference: Communication to WHO, 26 September 2001).
Cuba	January 2001	The Centre for State Control of Drug Quality in Cuba (CECMED) has banned the use of cisapride until its risk/ benefit ratio is further reviewed (Reference: CECMED Resolution No 1/2001, 8 January 2001. As communicated to WHO, 12 September, 2001).
Indonesia	30 June 2000	The Directorate General of Drug and Food Control has suspended the marketing authorization for cisapride and has withdrawn it from the market until the risk/benefit ratio is further reviewed because of the possibility of rare but serious heart complications including arrhythmias and sudden death (Reference: Communication to WHO, 13 September 2001).
	October 2000	The Directorate General of Drug and Food Control has allowed the marketing authorization for 5 mg cisapride with restrictions on indication, dosage, access and distribution. Availability has been restricted to only a few hospitals, with close monitoring for adverse reactions (Reference: Communication to WHO, 13 September 2001).
Singapore	September 2000	The product licences for all cisapride containing preparations were suspended by the National Pharmaceutical Administration, Ministry of Health, Singapore in September 2000 following reports of increased risk of serious cardiac arrhythmia. Cisapride may still be made available on an individual basis (Reference: Communication to WHO, 19 September 2001).
Thailand	June 2001	Severely restricted for prescription use by gastrointestinal physicians and limited use in gastro-esophageal-reflux-disease patients only (Reference: Communication to WHO, 28 September 2001).
Turkey	May 2000	General Directorate of Pharmaceuticals and Pharmacy of the Ministry of Health has withdrawn cisapride from the market because of serious cardiovascular adverse effects seen in the world (Reference: FDA Talk Paper, 14 July 2000. As communicated to WHO, 20 September 2001).

Product Name: **Clobenzorex**

CAS number: 13364-32-4

Scientific and Common Names, Synonyms:

(+)-N-(o-Chlorobenzyl)-α-methylphenethylamine;

Asenlix, Finedal

Country	Effective Date	Description of action taken Grounds for decision
Mauritius	August 2000	Removed from the market following a similar decision of the Agence Française de Sécurité Sanitaire des Produits de Santé in respect of appetite suppressants in September 1999 (Reference: Communication to WHO, 27 August 2001).

Product Name: Codeine

CAS number: 76-57-3

Scientific, Common Names, Synonyms:

6-Hydroxy-3-methoxy-N-methyl-4,5 epoxymorhin-7-ene;

Methylmorphin, Codicept, Codol

Country	Effective Date	Description of action taken Grounds for decision
Mauritius	August 2001	All codeine based products have been moved to the prescription-only status. Import of these products require authorization from the Ministry of Health. Importers and distributors are required to submit monthly returns of sales (Reference: Communication to WHO, 27 August 2001).

Product Name: Dexfenfluramine

CAS number: 3239-44-9

Scientific, Common Names, Synonyms:

(S)-N-Ethyl-α-methyl-3-(trifluoromethyl)benzeneethanamine;

d-Fenfluramine, Diomeride

Country	Effective Date	Description of action taken Grounds for decision
Brazil	August 2001	Registration has been cancelled due to risks of heart valve disorders (Reference: Resoluçao n. 147/ANVISA, 08/14/2001. As communicated to WHO, 13 September 2001).

Product Name: Dextromethorphan

CAS number: 125-71-3

Scientific and Common Names, Synonyms:

(9α,13α,14α)-3-Methoxy-17-methylmorphinan;

Dextophan, Dextrophen, Agrippol

Country	Effective Date	Description of action taken Grounds for decision
Oman	June 2001	All preparations containing dextramethorphan, either alone or in combination, have been classified as controlled non-psychotropic

		drugs. This action was taken to ensure that the drug is not misused, in view of a huge increase in its consumption in the form of cough preparations etc. (Reference: Ministry of Health, Directorate of Pharmaceuticals Affairs and Drug Control Circular No. 22/2001. As communicated to WHO, 22 July 2001).

Product Name: Dinoprostone

CAS number: 363-24-6

Scientific and Common Names, Synonyms:

(5Z,11α,13E,15S)-11,15-Dihyroxy-9-oxoprosta-5,13-dien-1-oic acid;

Prostaglandin E2, Minprostin, Prostenon

Country	Effective Date	Description of action taken Grounds for decision
Thailand	April 2001	Severely restricted for use as a prescription drug in hospitals only (Reference: Communication to WHO, 28 September 2001).

Product Name: Doxycycline

CAS number: 564-25-0

Scientific and Common Names, Synonyms:

4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide;

Doxycyl

Country	Effective Date	Description of action taken Grounds for decision
France	February 2001	The gel form of doxycycline preparations remain suspended in France due to frequent associations of adverse effects on the oesophagus (Reference: Communication to WHO, 5 October 2001).

Product Name: Droperidol

CAS number: 548-73-2

Scientific and Common Names, Synonyms:

1-[1-[4-(4-Fluorophenyl)-4-oxobutyl]-1,2,3,6-tetrahydro-4-pyridinyl]-1,3-dihydro-2*H*-benzimidazol-2-one;

Dehydrobenzperidol, Inopsin, Diaperidol

Country	Effective Date	Description of action taken Grounds for decision
Indonesia	June 2001	The National Agency for Drug and Food Control (NADFC) has suspended the marketing authorization of droperidol because of serious cardiac adverse effects (Reference: Communication to WHO, 13 September 2001).
UK	March 2001	Droperidol has been withdrawn in the UK following concerns about serious cardiac adverse effects (Reference: Medicines Control Agency, Important Safety Messages, 11 January 2001. Available from URL: http://www.open.gov.uk).

Product Name: Etanercept

CAS number: 185243-69-0

Scientific and Common Names, Synonyms:

1-235-Tumor necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G1 (human γ1-chain Fc fragment) dimer ;

Enbrel, γhu TNFR:Fc, Tanercept

Country	Effective Date	Description of action taken Grounds for decision
Chile	October 2001	The Public Health Institute of Chile has modified the labels to include warnings about the adverse reactions that affect the central nervous system and the haematological system (Reference: Communication to WHO, 26 September 2001).

Product Name: Ethambutol

CAS number: 74-55-5

Scientific and Common Names, Synonyms:

[S-(R*, R*)]-2,2[1]-(1,2-Ethanediyldiimino)bis(1-butanol);

Aethambutolum, Embutol, Etbutol

Country	Effective Date	Description of action taken Grounds for decision
Thailand	October 2000	Warning about the risk of loss of eyesight (Reference: Communication to WHO, 28 September 2001).

Product Name: Ethanol

CAS number: 64-17-5

Scientific and Common Names, Synonyms:

Ethyl alcohol, Alcohol aethylicus

Country	Effective Date	Description of action taken Grounds for decision
Brazil	April 2001	The National Health Surveillance Agency has prohibited the inclusion of ethanol in pharmaceutical preparations (Reference: Resoluçao n.543/ANVISA, 04/19/2001. As communicated to WHO, 13 September 2001).

Product Name: Etretinate

CAS number: 54350-48-0

Scientific and Common Names, Synonyms:

(*all-E*)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid ethyl ester;

Ro 10-9359, Tigason

Country	Effective Date	Description of action taken Grounds for decision
Brazil	February 2001	Use and sale banned because of dangerous side effects, mainly myopathy (Reference: Communication to WHO, 13 September 2001).

Product Name: Famotidine

CAS number: 76824-35-6

Scientific and Common Names, Synonyms:

3-[[[2-[(Aminoiminomethyl)amino]-4-thiazolyl]methyl]thio-*N*-(aminosulfonyl)propanimidamide;

Amifatidine, Pepsidac, Famodil

Country	Effective Date	Description of action taken Grounds for decision

Thailand	April 2001	To be used with precaution, especially in renal patients (Reference: Communication to WHO, 28 September 2001).

Product Name: Gallopamil

CAS number: 1662-47-8

Scientific and Common Names, Synonyms:

∝[3-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]propyl]-3,4,5-trimethoxy-α-(1-methyl-ethyl)benzeneacetonitrile;

Methoxyverapamil, Corapamil, Benpredil

Country	Effective Date	Description of action taken Grounds for decision
Turkey	May 2001	The General Directorate of Pharmaceuticals and Pharmacy of the Ministry of Health suspended the marketing authorization of gallopamil because of the decision of the Registration Committee (Reference: Communication to WHO, 20 September 2001).

Product Name: Gamelonic acid

Scientific and Common Names, Synonyms:

Primrose oil derivative;

Epogam, Efamast

Country	Effective Date	Description of action taken Grounds for decision
UK	October 2002	The Medicines Control Agency has withdrawn the marketing authorizations for two gamelonic acid containing derivatives (Epogam, Efamast) of primrose oil, originally licensed for the symptomatic relief of eczema in children, due to inadequate standards of efficacy with these products. However, since no safety issues are involved, these products will continue to be available in health food shops as dietary supplements (Reference: News Update. Available from URL: http://www.mca.gov.uk/whatsnew).

Product Name: Glutoxim

Country	Effective Date	Description of action taken Grounds for decision

Armenia	September 2000	The Armenian Drug and Medical Technology Agency did not approve the marketing of the new immunomodulating agent on grounds of doubtful safety and incomplete clinical trial (Reference: Communication to WHO, 31 August 2001).

Product Name: Hexestrol

CAS number: 5635-50-7

Scientific and Common Names, Synonyms:

4-4[1]-(1,2-Diethyl-1,2-ethanediyl)bis[phenol];

Synoestrolum, Dihydrodiethylstilbestrol

Country	Effective Date	Description of action taken Grounds for decision
Armenia	September 2000	The Armenian Drug and Medical Technology Agency did not approve the marketing of this product on grounds of risk of carcinogenicity and withdrew the product from the entire market (Reference: Communication to WHO, 31 August 2001).

Product Name: Hyaluronidase

CAS number: 9001-54-1

Scientific and Common Names, Synonyms:

Hylase, Diffusin

Country	Effective Date	Description of action taken Grounds for decision
Slovak Republic	June 2001	Injections for intramuscular or subcutaneous use were withdrawn from sale nationally because of incomplete data on BSE risk (Reference: Communication to WHO, 24 August 2001).

Product Name: Levacetylmethadol

CAS number: 34433-66-4

Scientific and Common Names, Synonyms:

(-)-6-(Dimethylamino)-4,4-diphenyl-3-heptanol acetate (ester);

Orlaam, Levomethadylacetate

Country	Effective Date	Description of action taken Grounds for decision
Europe	2001	The European Medicines Evaluation Agency (EMEA) has recommended the suspension of the marketing authorization of levacetylmethadol (Orlaam) in view of its pro-arrhythmic potential and the fact that a re-assessment of the risk-benefit profile showed no special advantage for levacetylmethadol over existing alternatives (Reference: EMEA Public Statement EMEA/8776/01, 19 April 2001. Available from URL: http://www.emea.eu.int).

Product Name: **Lindane**

CAS number: 58-89-9

Scientific and Common Names, Synonyms:

(1α,2α,3β,4α,5α,6β)-Hexachlorocyclohexane;

Benhexachlor, Gamma benzene hexachloride, Gamex

Country	Effective Date	Description of action taken Grounds for decision
Brazil	February 2001	The marketing authorization for products containing lindane was withdrawn because of unacceptable potential to cause toxic effects (Reference: Resoluçao n.147, 08/14/2001. As communicated to WHO, 13 September 2001).

Product Name: **Lipoic acid**

CAS number: 1077-28-7

Scientific and Common Names, Synonyms:

1,2-Dithiolane-3-pentanoic acid;

Thioactacid, Liposan

Country	Effective Date	Description of action taken Grounds for decision
Armenia	February 2001	The Armenian Drug and Medical Technology Agency has not approved marketing of the new immunomodulating agent on the grounds of unacceptable risk benefit ratio resulting from serious adverse effects (Reference: Communication to WHO, 31 August 2001).

Product Name: Metamizole sodium

CAS number: 50567-35-6

Scientific and Common Names, Synonyms:

[(2,3-Dihydro-1,5-dimethyl-3-oxo-2-phenyl-1*H*-pyrazol-4-yl) methylamino methanesulfonic acid;

Analgin, Dipyrone

Country	Effective Date	Description of action taken Grounds for decision
Lithuania	September 2000	The marketing authorization for tablets was not renewed for safety reasons (Reference: Decision of Medicines Registration Centre, 22 September 2000. As communicated to WHO, 24 August 2001).

Product Name: Miglustat

CAS number: 72599-27-0

Scientific and Common Names, Synonyms:

1,5-(Butylimino)-1,5-dideoxy-D-glucitol;

Vevesca

Country	Effective Date	Description of action taken Grounds for decision
Israel	2002	Miglustat has been temporarily withdrawn in Israel as a precaution pending investigation of an unexplained cognitive dysfunction in a patient previously treated with the drug (Reference: Media Release, 24 April 2002. Available from URL: http://www.ogs.com).

Product Name: Misoprostol

CAS number: 59122-46-2

Scientific and Common Names, Synonyms:

(11α,13E)-11,16-Dihydroxy-16-methyl-9-oxoprost-13-en-1-oic acid methyl ester

Cyprostol, Oxaprost, Prostalgin

Country	Effective Date	Description of action taken Grounds for decision

Thailand	October 2000	This drug has been severely restricted for use in hospitals only (Reference: Communication to WHO, 28 September 2001).

Product Name: Nevirapine

CAS number: 129618-40-2

Scientific and Common Names, Synonyms:

11-Cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2^{1},3^{1}-e][1,4]diazepin-6-one;

Viramune, Nevimune

Country	Effective Date	Description of action taken Grounds for decision
Thailand	February 2001	Precautionary note added about hepatotoxicity (Reference: Communication to WHO, 28 September 2001).

Product Name: Nimesulide

CAS number: 51803-78-2

Scientific and Common Names, Synonyms:

N-(4-Nitro-2-phenoxyphenyl)methanesulfonamide;

Nimulid

Country	Effective Date	Description of action taken Grounds for decision
Spain	May 2002	The Spanish Committee on Safety of Medicines has recommended the temporary suspension of nimesulide pending evaluation of reports of hepatotxicity with the drug by the European Agency for the Evaluation of Medicinal Products (Reference: Communication on Drug Risks, No. 2002/03, 3 May 2002. Available from URL: http://www.msc.es/agemed/).

Product Name: Oxytocin

CAS number: 50-56-6

Scientific and Common Names, Synonyms:

L-Cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide cyclic (1→6)-disulfide;

Pituitrin, Oxytocin

Country	Effective Date	Description of action taken Grounds for decision
Mauritius		Oxytocin injections have been restricted for use only in public and private hospitals with maternity units and will no longer be available in retail pharmacies (Reference: Communication to WHO, 27 August 2001).

Product Name: Paracetamol

CAS number: 103-90-2

Scientific and Common Names, Synonyms:

p-(Acetylamino)phenol;

Acetaminophen, Anacin, Crocin, Tylenol

Country	Effective Date	Description of action taken Grounds for decision
Thailand	February 2001	Precautions in children dosage for paracetamol drop formulation have been revised (Reference: Communication to WHO, 28 September 2001).

Product Name: Phenobarbital

CAS number: 50-06-6

Scientific and Common Names, Synonyms:

5-Ethyl-5-phenyl-2,4,6(1H,3H,5H)-pyrimidinetrione;

Gardenal, Luminal

Country	Effective Date	Description of action taken Grounds for decision
France	April 2001	Phenobarbital has been suspended due to reports of rare but severe cutaneous and mucosal reactions including Lyell Syndrome and Stevens-Johnson syndrome (Reference: Communication to WHO, 5 October 2001).
Mauritius	2001	Based on the French regulatory action, all phenobarbital preparations other than those used as anti-epileptic products are being phased out of the market in Mauritius. Further import permits have not been issued (Reference: Regulatory decision taken by the Agence Française de Sécurité des Produits de Santé on 21 February 2001 on phenobarbitone preparations used as mild sedatives. As communicated to WHO, 27 August 2001).

Product Name: Phenol

CAS number: 108-95-2

Scientific and Common Names, Synonyms:

Hydroxybenzene;

Carbolic acid, Phenylic acid

Country	Effective Date	Description of action taken Grounds for decision
Lithuania	December 2000	Phenol aerosol was not granted marketing authorization on the grounds that other safer antiseptics are now available (Reference: Decision of the Medicines Registration Centre of the State Medicines Control Agency, 5 December 2000. As communicated to WHO, 24 August 2001).

Product Name: Phenylpropanolamine

CAS number: 14838-15-4

Scientific and Common Names, Synonyms:

DL-*erythro*-2-Amino-1-phenyl-1-propanol;

Norephedrine, Apoephedrine

Country	Effective Date	Description of action taken Grounds for decision
Brazil	November 2000	The National Health Surveillance Agency stopped the sale of all products containing phenylpropanolamine due to the potential of these products to induce several adverse reactions including cerebral haemorrhage (Reference: Resoluçao n.96/MS/ANVS, 11/10/2000. As communicated to WHO, 13 September 2001).
Canada	2001	Health Canada has directed the removal of all phenylpropanolamine containing products from the Canadian market due to the risk of serious haemorrhagic strokes with phenylpropanoloamine (Reference: Health Canada Advisory, May 2001. Available from URL: http://www.hc-sc.gc.ca).
Chile	October 2001	The Public Health Institute of Chile has modified the labels of products containing phenylpropanolamine, warning against their use in children under the age of 12 years and advising patients to immediately report to their physicians all adverse reactions experienced with phenylpropanolamine products (Reference: Communication to WHO, 26 September 2001).

Cuba	May 2001	The Centre for State Control of Drug Quality (CECMED) issued a resolution banning the use of phenylpropanolamine products in Cuba (Reference: CECMED Resolution No 7/2001 dated 16 May, 2001. As communicated to WHO, 12 September 2001).
Indonesia	April 2001	The National Agency for Drug and Food Control (NADFC) in Indonesia has allowed the marketing of phenylpropanolamine containing products with restrictions on the maximum strength per unit dose and maximum daily dose (adult 15 mg/unit dose; 60 mg per day; children 7.5 mg/unit dose; 30 mg per day) (Reference: Communication to WHO, 13 September 2001).
Lithuania	November 2000	The classification status of all medicinal products containing phenylpropanolamine was changed from over-the-counter (OTC) to prescription-medicines-only (PMO). Restrictions in dosage (not to exceed 100 mg daily dose) and contraindications (not to be used in patients with arterial hypertension, atherosclerosis of cerebral arteries and in patients on concurrent anticoagulant therapy) and dosage adjustment in children were recommended. Usage in children below 12 years of age was banned (Reference: State Medicines Control Agency order No 136, 16 Nov 2000; LSMCA bulletin 'Pharmacon' No. 24, 2000. As communicated to WHO, 17 August 2001).
Malaysia	November 2000	The Ministry of Health suspended the registration of all medicines containing phenylpropanolamine (PPA) following a US report of increased risk of haemorrhagic stroke in people taking medicines containing PPA (Reference: Communication to WHO, 5 October 2001).
Oman	December 2000	The registration of all products containing phenylpropanolamine has been cancelled in Oman (Reference: Ministry of Health Circular No 64/2000. As communicated to WHO, 2 October 2001).
Singapore	November 2000	Manufacturers were asked to withdraw all products containing phenylpropanolamine (PPA) from the market following reports of increased risk of haemorrhagic stroke. Manufacturers have been advised to re-formulate their products without PPA (Reference: Communication to WHO, 19 September 2001).
UK	December 2000	The Committee on Safety of Medicines (CSM) concluded that the evidence of a link between haemorrhagic stroke and phenylpropanolamine (PPA) is weak and recommended that the Medicines Control Agency should work closely with manufacturers to improve existing product information on the packs and patient information leaflets for PPA containing products with more prominent warnings (Reference: Safety Message Update. Available from URL: http://www.mca.gov.uk).
USA	November 2000	All phenylpropanolamine (PPA) containing products were withdrawn due to risk of haemorrhagic stroke after a research study by scientists at Yale University showed a significant increase in the risk for haemorrhagic strokes among women who had taken PPA as an appetite suppressant (Reference: Public Health Advisory issued on November 6, 2000. Available from URL: http://www.fda.gov).

Product Name: Propofol

CAS number: 2078-54-8

Scientific and Common Names, Synonyms:

2,6-Diisopropylphenol;

Diprivan, Disoprofol

Country	Effective Date	Description of action taken Grounds for decision
Lithuania	March 2001	The State Medicines Control Agency of Lithuania (SMCA) has further extended the restrictions on the use of propofol. The agency has advised that propofol is not a recommended drug and should not be used for sedation in children below the age of 16 years (Reference: SMCA order NO 43, 23 March 2001; LSMCA bulletin 'Pharmacon', No 5-6, 2001. As communicated to WHO, 17 September 2001).

Product Name: Sildenafil

CAS number: 139755-83-2

Scientific and Common Names, Synonyms:

1-[[3-(4,7-Dihydro-1-methyl-7-oxo-3-propyl-1-*H*-pyrazolo[4,3- d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine;

Viagra, Segurex

Country	Effective Date	Description of action taken Grounds for decision
Chile	September 2001	The Public Health Institute of Chile modified the labels to include the information that a medical evaluation is needed before administering this medication (Reference: Communication to WHO, 26 September 2001).

Product Name: Strychnine

CAS number: 57-24-9

Scientific and Common Names, Synonyms:

Strychnidin-10-one

Country	Effective Date	Description of action taken Grounds for decision

Brazil	February 2001	Registration of combination products containing strychnine are banned because of the potential to cause convulsions (Reference: Resoluçao n. 147/ANVISA, 08/14/2001. As communicated to WHO, 13 September 2001).

Product Name: Sulprostone

CAS number: 60325-46-4

Scientific and Common Names, Synonyms:

[1R-[1α(Z),2β(1E,3R*),3α]]-7-[3-Hydroxy-2-(3-hydroxy-4-phenoxy-1-butenyl)-5-oxocyclopentyl]-N-(methylsulfonyl)-5-heptenamide;

CP-34089, Nalador

Country	Effective Date	Description of action taken Grounds for decision
Thailand	April 2001	Severely restricted prescription drug to be used in hospitals only (Reference: Communication to WHO, 28 September 2001).

Product Name: Tartrazine colouring agent

CAS number: 60325-46-4

Scientific and Common Names, Synonyms:

Country	Effective Date	Description of action taken Grounds for decision
Oman	March 2002	The Directorate General of Pharmaceutical Affairs and Drug Control has banned the use of Tatrazine FD&C Yellow No. 5 in pharmaceutical products, in any pharmaceutical form, following similar restrictions worldwide due to a spectrum of side effects such as allergies, thyroid tumors, lymphocytic lymphomas, chromosomal damage, asthma attacks, urticaria and hyperactivity (Reference: Circular No. 50/2001, dated 12 November, 2001. As communicated to WHO, 15 January 2002).

Product Name: Terfenadine

CAS number: 50679-08-8

Scientific and Common Names, Synonyms:

α-[4-(1,1-Dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol;

Antifen, Fenadin

Country	Effective Date	Description of action taken Grounds for decision
Chile	March 2001	The Public Health Institute of Chile has banned the use of terfenadine due to serious cardiotoxic effects reported in conjunction with other drugs (Reference: Communication to WHO, 26 September 2001).
Brazil	July 2000	Withdrawn from the Brazilian market due to the increased risk of producing cardiac arrhythmias (Reference: Resoluçao n.67/MS/ANVS 07/17/2000. As communicated to WHO, 13 September 2001).

Product Name: **Thiomersal**

CAS number: 148-61-8

Scientific and Common Names, Synonyms:

Ethyl(2-mercaptobenzoato-S)mercury;

Thiobactal

Country	Effective Date	Description of action taken Grounds for decision
Brazil	June 2001	Products containing thiomersal are prohibited except those intended for vaccine conservation (Reference: Resoluçao n.528/ANVISA, 006/08/2001. As communicated to WHO, 13 September 2001).
Malaysia		The Drug Control Authority in Malaysia has directed manufacturers to discontinue the use of thiomersal as a preservative in vaccines and to replace it with other permitted preservatives (Reference: Newsletter of the Drug Control Authority, Malaysia, vol. 18, No 2, August 2001. As communicated to WHO, 5 October 2001).

Product Name: **Tianeptine**

CAS number: 66981-73-5

Scientific and Common Names, Synonyms:

7-[(3-Chloro-6,11-dihydro-6-methyldibenzo[c,f][1,2]thiazepin-11-yl)amino]heptanoic acid S,S-dioxide;

Coaxil, Stablon

Country	Effective Date	Description of action taken Grounds for decision

Bahrain		The Drug Control Directorate has classified tianeptine sodium under the 'special-drugs-under-controlled prescriptions' category due to increasing reports of misuse and abuse by patients (Reference: Communication to WHO, 20 August 2001).

Product Name: Troglitazone

CAS number: 97322-87-7

Scientific and Common Names, Synonyms:

5-[p-[(6-Hydroxy-2,5,7,8-tetramethyl-2-chromanyl)methoxy]benzyl]-2,4-thiazolidinedione;

Rezulin, Ronglitazone

Country	Effective Date	Description of action taken Grounds for decision
Chile	October 2000	Use in formulations has been banned by the Public Health Institute of Chile; the marketing authorization has been cancelled (Reference: Communication to WHO, 26 September 2001).

Product Name: Trypsin

CAS number: 9002-07-7

Scientific and Common Names, Synonyms:

Parenzyme, Trypsillin

Country	Effective Date	Description of action taken Grounds for decision
Slovak Republic	June 2001	Injections for intramuscular use were not approved because of incomplete data on safety and efficacy (Reference: Communication to WHO, 24 August 2001).

Product Name: Valproic acid

CAS number: 99-66-1

Scientific and Common Names, Synonyms:

2-Propylpentanoic acid;

Vederon, Valproine

Country	Effective Date	Description of action taken Grounds for decision

Chile	November 2001	The Public Health Institute of Chile has modified the labels to include warnings about the adverse reactions (pancreatitis and its symptoms) associated with the drug (Reference: Communication to WHO, 26 September 2001).

Product Name: Boric Acid and borates

CAS number: 10043-35-3

Country	Effective Date	Description of action taken Grounds for decision
Brazil	April 2001	Boric acid and borax have been eliminated from preparations for topical administration in infants (Reference: Resoluçao n.552/ANVISA, 04/30/2001. As communicated to WHO, 13 September 2001).

Product Name: Gangliosides

Country	Effective Date	Description of action taken Grounds for decision
Brazil	June 2001	Registration has been cancelled due to association with cases of Guillain-Barré Syndrome. Some cases were fatal (Reference: Resoluçao/ANVISA n.527, 06/08/2001. As communicated to WHO on 13 September 2001).

Product Name: Herbal Dietary Supplements

Country	Effective Date	Description of action taken Grounds for decision
Canada Ireland USA	February 2002	The manufacturer has issued a product recall for herbal medicines PC-SPES and SPES since these products were found to contain warfarin and alprazolam, respectively. Consumers have been advised to stop using these products and consult their physicians (References: Health Canada Warnings / Advisories, 8 February 2002, available from URL: http://www.hc-sc.gc.ca; Current News and IMB Statements, 15 February 2002, available from URL: http://www.imb.ie; Warning from the Office of Public Affairs, California, Department of Health Services, February 2002; available from URL: http://www.fda.gov).

Product Name: Kava products

Country	Effective Date	Description of action taken Grounds for decision

Australia	August 2002	Australia's Therapeutic Goods Administration (TGA) has initiated a voluntary recall of all complementary medicines containing the herb kava. The action follows the death of a woman in Australia who used a medicine containing kava. The TGA will under take further evaluation to determine additional regulatory measures (Reference: TGA's Media Release TW20/02, 15 August 2002).
Canada	August 2002	Health Canada has ordered a stop-sale and recall of all kava-containing products from the Canadian market following Candian and worldwide reports of liver failure (Reference: Health Canada Warnings and Advisories, 21 August 2002).
Germany	June 2002	The Federal Institute of Germany has withdrawn all kava containing pharmaceutical products and homeopathic products with dilutions up to D4 due to hepatotoxic risks and insufficient data on efficacy with these products (Reference: Communication to WHO, 17 June 2002).
Ireland	July 2002	The Irish Medicines Board has decided to maintain the on-going voluntary withdrawal of all kava containing products that was initiated in February 2002. This decision follows the German Regulatory Authority's conclusion that kava products have an unfavourable risk-benefit profile (Reference: Kava Kava statement by the pharmaceutical Society of Ireland, available from URL: http://www.pharmaceuticalsociety.ie).
Singapore	July 2002	The Singapore Health Sciences Authority (HAS) is proceeding to gazette kava-kava and its constituents under the Poisons Act to prohibit importation following German Regulatory measures for kava (Reference: Singapore Health Sciences Authority Press Release, 25 July 2002).
Switzerland	April 2001	Acetone extract of kava root was withdrawn due to unfavourable benefit-risk profile and associations with hepatic injury.
	September 2001	Kava ethanol extract products have been moved from OTC to 'pharmacy only' status as a precautionary measure (Reference: Press Release, June 2002, available from http//:www.swissmedic.ch).
UK	December 2002	An order prohibiting the supply of medicinal products containing kava has been issued in the UK following the UK Medicines Control Agency's investigation into cases of liver toxicity from kava (Reference: MCA Press Release 2002 / 0528, 20 December 2002).

Product Name: **Phlebotonics**

Country	Effective Date	Description of action taken Grounds for decision
Spain	September 2002	The Spanish Medicines Agency has withdrawn the marketing authorization for several oral vascular disorder therapies (phlebotonics) including those containing diosmin, horse chestnut extract, naftazone and troxerutin because of unfavourable risk-benefit profile. Calcium dobesilate has been restricted to the treatment of diabetic retinopathy while all other oral vascular therapies remaining

on the market are authorized only for the short-term relief (2-3 months) of oedema and other symptoms of chronic venous insufficiency (Reference: Spanish Medicines Agency Document 2002/09, 10 September 2002).

Product Name: Allopurinol and Benzbromarone

Country	Effective Date	Description of action taken Grounds for decision
France	February 2001	This anti-gout preparation has been withdrawn in France due to associations of adverse hepatic effects with benzbromarone and toxic skin and hypersensitivity reactions with allopurinol (Reference: Communication to WHO, 5 October 2001).

Product Name: Calcium bromidum and Chloral hydrate

Country	Effective Date	Description of action taken Grounds for decision
France	August 2001	Withdrawn due to the mutagenic and carcinogenic potential of chloral hydrate (Reference: Communication to WHO, 5 October 2001).

Product Name: Fluphenazine and Nortriptyline

Country	Effective Date	Description of action taken Grounds for decision
France	2000	This combination was suspended due to unfavourable risk / benefit ratio; the combination of the neuroleptic agent and the antidepressant provided no special advantage while exposing the patients to unjustifiable risk (Reference: Communication to WHO, 5 October 2001).

Product Name: Lidocaine, Salicylic acid and Chloral hydrate

Country	Effective Date	Description of action taken Grounds for decision
France	August 2001	Withdrawn due to the mutagenic and carcinogenic potential of chloral hydrate which make its use unfavourable in the treatment of buccal infections or as an oral rinse in stomatologic procedures (Reference: Communication to WHO, 5 October 2001).

Product Name: Phenobarbital, Difebarbamate and febarbamate (Tetrabamate)

Country	Effective Date	Description of action taken Grounds for decision
France	March 2001	The combination of febarbamate, difebarbamate and phenobaribital has been withdrawn in France due to reports of serious hepatic effects and cutaneous reactions including Lyell syndrome (Reference: Communication to WHO, 5 October 2001).
Spain	May 2002	The Spanish Committee on the Safety of Medicines has ordered the suspension of tetrabamate (a complex of phenobarbital, difebarbamate and febarbamate) due to reports of hepatotoxicity and unfavourable risk-benefit ratio (Reference: Communication on Drug Risks, No. 2002/04, 3 May 2002. Available from URL: http://www.msc.es/agemed/).

Product Name: **Xibornol and Lidocaine**

Country	Effective Date	Description of action taken Grounds for decision
France	April 2001	Suspended due to grave allergic reactions including oedema of Quincke, anaphylaxis and bullous eruptions associated with xibornol (Reference: Communication to WHO, 5 October 2001).