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PHARMACEUTICALS: RESTRICTIONS IN USE AND AVAILABILITY

March 2001

Essential Drugs and Medicines – Quality Assurance and Safety of Medicines
Health Technology and Pharmaceuticals
World Health Organization
Geneva, Switzerland

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have been Banned, Withdrawn, Severely Restricted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 – March 2001

Essential Drugs and Medicines – Quality Assurance and Safety of Medicines
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This text is the second 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to the Sixth Issue of the United Nations Consolidated List of Products whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments - Pharmaceuticals (UN General Assembly Resolutions 37/137, 1982; 38/149, 1983; 39/229, 1984; 44/226, 1989).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 2000.

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 41 governments on 76 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 licences 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.

Criteria for the inclusion of pharmaceutical products in the UN Consolidated List

a) ***Banned product***

A product that has been withdrawn from use and/or sale nationally in one or more countries by order of the competent national authority, having regard to its safety in relation to its intended use.

b) ***Voluntary withdrawal***

A product that has been withdrawn from use and/or sale nationally in one or more countries by voluntary action of the manufacturer, having regard to its safety in relation to its intended use.

c) ***Severely restricted***

A product containing:

(i) a substance that is controlled more rigorously than is provided for under the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances or that is subject to analogous control at the national level before it has been considered for international scheduling.

(ii) a substance that may be incorporated in pharmaceutical dosage forms only within the specific limits determined by statute.

(iii) a substance that is approved by a competent national authority and is subjected to restrictions that exclude its use in a substantial proportion of the potential target population of patients having regard to its safety. A substance which from the outset has been severely restricted in its indications having regard to the known balance of safety and efficacy is excluded.

d) ***Not approved***

A product that has been formally submitted for registration by a manufacturer to a national competent authority and which has been rejected on grounds of safety.

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Product name: **Alatrofloxacin mesilate**

CAS number: **157605-25-9**

Synonyms: 7-{(1R,5S,6s)-6-[(S)-2-Aminopropionamido)propionamido]-3-azabicyclo[3.1.0]hex-3-yl}-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid monomethanesulphonate

Country	Effective Date	Description of action taken Grounds for decision
Armenia	July 2000	The Drug and Medical Technology Agency have rejected registration of alatrofloxacin because recent studies have shown serious and unpredictable liver injuries after administration of the drug. (Reference: Communication to WHO, 9 August 2000)
Singapore		The National Pharmaceutical Administration in the Ministry of Health has not approved alatrofloxacin since it is associated with hepatic adverse reactions. (Reference: Communication to WHO, 2 August 2000.)

Product name: **Aldesleukin**

CAS number:

Synonyms: Interleukin-2; Epidermal thymocyte Activating Factor; T-cell Growth Factor

Country	Effective Date	Description of action taken Grounds for decision
Singapore		The National Pharmaceutical Administration in the Ministry of Health has restricted the use of aldesleukin to medical oncologists in view of life-threatening toxicities, which have been reported with the drug. (Reference: Communication to WHO, 2 August 2000.)

Product name: **Amineptine**

CAS number: **57574-09-1**

Synonyms: 7-[(10,11-Dihydro-5H-dibenzo{a,d}cyclohepten-5-yl)amino]hepatanoic acid hydrochloride

Country	Effective Date	Description of action taken Grounds for decision
Brunei Darussalam	June 1999	The Medical Health Services Headquarters in the Ministry of Health has withdrawn all tablets of amineptine (Survector) from the market with effect from 30 June 1999. (Reference: Official letter to Regulatory Agencies, Servier Singapore, February 1999.)
France	January 1999	The Medicines Agency has announced that the marketing authorization for the antidepressant, amineptine (SurvectorR: Servier) has been suspended and withdrawn in France. These actions have been taken after an evaluation of amineptine revealed a potential for abuse and risk of dependence. (Reference: Infofax Pharmacovigilance, Agence du Médicament, Saint-Denis, 22 January 1999.)
Italy	1999	
Morocco	June 1999	The National Advisory Commission for Pharmacovigilance has decided to suspend the marketing authorization for amineptine. This action is based on international data concerning the potential abuse and risk of dependence associated with the intake of this product. (Reference: Letter from the Directorate of Medicines and Pharmacy, Rabat, 24 August 1999.)
Oman	April 2000	The Directorate General of Pharmaceutical Affairs & Drug Control has rescheduled amineptine as a non-psychotropic restricted controlled item because of international data concerning its potential abuse and risk of dependence. (Reference Circular No. 25/2000 Directorate General of Pharmaceutical Affairs, Ministry of Health, Sultanate of Oman 25/4/2000.)
Thailand	January 1999	The Ministry of Health has withdrawn preparations of amineptine following action taken in France. (Reference: E-mail communication from the Food and Drug Administration, Ministry of Health, Bangkok, Thailand, 28 January 1999).
United Arab Emirates	12 January 1999	The Ministry of Health has banned the sale of amineptine on account of a potential for abuse and risk of dependence. (Reference: Communication with WHO, 10 July 2000.)
Viet Nam	August 1999	The Drug Administration of Viet Nam in the Ministry of Health has withdrawn approval for the antidepressant, amineptine (Survector). This follows the decision taken by France to suspend amineptine on the basis of abuse and dependency potential. (Reference: Directive from Ministry of Health, Drug Administration of Viet Nam, No. 41/1999/QD-QLD, 5 August 1999.)

Product name: **Amfepramone hydrochloride**

CAS number: **134-80-5**

Synonyms: Dethylpropion hydrochloride

Country	Effective Date	Description of action taken Grounds for decision
United Kingdom	April 2000	The Medicines Control Agency has banned the anorectic agent, amfepramone hydrochloride on the basis of a European Commission decision stating that risks outweigh the benefits. (Reference: Communication to WHO, 30 August 2000 from the Medicines Control Agency, Department of Health, United Kingdom.)

Product name: **Aristolochia**

CAS number:

Synonyms:

Country	Effective Date	Description of action taken Grounds for decision
United Kingdom	July 1999	The Medicines Control Agency has banned the import, sale and supply of medicinal products containing the Chinese herbal medicine Aristolochia. This was on account of end-stage renal failure associated with the use of this product. (Reference: Statutory Instrument no. 2889 The Medicines (Aristolochia) (Temporary Prohibition) Order 1999 which came into force 28 October 1999.)

Product name: **Astemizole**

CAS number: **68844-77-9**

Synonyms: 1[(4-fluorophenyl)methyl]-N-[1-[2-(4-methoxyphenyl)ethyl]- 4-piperidinyl]-1H-benzimidazol-2-amine

Country	Effective Date	Description of action taken Grounds for decision
Armenia	July 2000	Astemizole has been voluntarily withdrawn on the basis of prolongation of the QT-interval and ventricular arrhythmias. (Reference: Communication to WHO, 9 August 2000)
Brunei Darussalam	July 1999	The manufacturer withdrew astemizole worldwide because of serious adverse cardiovascular reactions. (Reference: Official letter to Regulatory Agencies, Jansses-Cilag, 1 July 1999.)

Mauritius	June 1999	Astemizole was withdrawn from the market following reports of adverse drug reactions published by the FDA and the decision of Janssen Pharmaceutica to remove the drug in the USA. (Reference: Letter to WHO from the Ministry of Health and Quality of Life, Port Louis, Mauritius, 27 December 2000.)
Philippines	1998	The Department of Health Bureau of Food and Drugs have noted the voluntary withdrawal by the sponsoring company of the antihistamine, astemizole due to its association with severe cardiac adverse events when used inappropriately with contraindicated drugs. (Reference: Communication from the Department of Health and Bureau of Food and Drugs to WHO, 15 August 2000.)
Singapore		The National Pharmaceutical Administration in the Ministry of Health has banned astemizole since it has been associated with adverse drug reactions including irregular heart rhythms and severe allergic reactions if taken at higher than recommended doses or in conjunction with some other drugs including antihypertensives and anti-asthmatics. (Reference: Communication to WHO, 2 August 2000.)
South Africa	1999	The South African Medicines Control Council has withdrawn products containing astemizole because of the potential for serious drug interactions. (Reference: Information from the Pharmaceutical Services in the Ministry of Health in South Africa.)
Tanzania	2 July 1999	The Pharmacy Board of the Ministry of Health, in the United Republic of Tanzania has withdrawn astemizole from the market. (Reference: Communication to WHO from the Ministry of Health, Tanzania, 20 November 2000.)
United Kingdom	1998	Astemizole has been reclassified to Prescription only Medicine as a result of new data on interactions from postmarketing surveillance studies. These data highlight an increased risk of QT prolongation with concomitant administration of oral or parenteral formulations of azole antifungals, macrolide antibiotics except azithromycin, selective serotonin reuptake inhibitors, HIV protease inhibitors and mibefradil (now withdrawn worldwide). In addition, astemizole is contraindicated for use in patients with hepatic dysfunction. (Reference: The Pharmaceutical Journal 261, p.9, 4 July 1998.)
United Arab Emirates	June 1999	The Ministry of Health has banned the sale of astemizole with effect from 23 June 1999 on account of increased risk of QT prolongation with concomitant administration of oral or parenteral formulations of azole antifungals, macrolide antibiotics except azithromycin, selective serotonin reuptake inhibitors and HIV protease inhibitors. (Reference: Communication with WHO, 10 July 2000
USA	1999	Janssen, the manufacturer of the histamine H1-receptor antagonist, astemizole, (HismanalR) has announced that it is voluntarily withdrawing the 10-mg formulation from the market. Since the drug's approval in 1988, new adverse reaction data has necessitated a series of labelling changes and warnings. In the light of the choices of other prescription antihistamines now available and the overall risk benefit profile of this drug,

		the Food and Drug Administration supports the decision of the company to withdraw the product. (Reference: FDA Talk Paper T99-29, 21 June 1999.)

Product name: **Bromfenac**

CAS number: **91714-94-2**

Synonyms: AHR-10282; Sodium[2-amino-3-(p-bromobenzoyl)phelyl]acetate sesquihydrate

Country	Effective Date	Description of action taken Grounds for decision
Saudi Arabia	June 1999	The Ministry of Health has withdrawn from the market products containing bromfenac because of reports of liver failure, sometimes fatal. (Reference: Communication from the WHO Regional Office for the Eastern Mediterranean enclosing a notification from the Ministry of Health, Saudi Arabia, 20 June 1999.)
USA	June 1998	Wyeth Ayerst Laboratories have voluntarily withdrawn from the market capsules of bromfenac sodium, a nonsteroidal anti-inflammatory analgesic indicated for the short-term management of acute pain. This action was taken on the basis of reports of severe hepatic failure resulting in four deaths and 8 liver transplants. (Reference: Federal Register 64 (44): 10944-10947, 1999.)

Product name: **Buprenorphine**

CAS number: **52485-79-7**

Synonyms: 21-cyclopropyl-7-alpha-(S)-1-hydroxy-1,2,2-trimethylpropyl)-6,14-endo-ethano-6,7,8,14-tetrahydro-oripavine

Country	Effective Date	Description of action taken Grounds for decision
Mauritius	2000	The Ministry of Health and Quality of Life has listed buprenorphine as a Schedule II medicine under the new Dangerous Drugs Act 2000. This is because abuse of the drug by intravenous as opposed to oral use has been reported to cause a number of deaths. (Reference: Letter to WHO from the Ministry of Health and Quality of Life, Port Louis, Mauritius, 27 December 2000.)

Product name: **Buspirone hydrochloride**

CAS number: **33386-08-2**

Synonyms: 8-[4-(4-Pyrimidin-2-ylpiperazin-l-yl)butyl]-8-azaspiro[4,5]decane-7,9-dione hydrochloride

Country	Effective Date	Description of action taken Grounds for decision
Mauritius	May 2000	The Ministry of Health and Quality of Life has rescheduled the antipsychotic agent buspirone into Schedule III of the consolidated Dangerous Drugs Act 2000 following observations of irrational use and emerging abuse. (Reference: Letter to WHO from the Ministry of Health and Quality of Life, Port Louis, Mauritius, 27 December 2000.)

Product name: **Camphor**

CAS number: **76-22-2**

Synonyms: Alcanfor; 2-Camphanone; Camphora

Country	Effective Date	Description of action taken Grounds for decision
South Africa	1999	The South African Medicines Control Council has removed camphor from all medicines unless efficacy data is submitted. (Reference: Information from the Pharmaceutical Services in the Ministry of Health in South Africa.)

Product name: **Chlormezanone**

CAS number: **80-77-3**

Synonyms: Chlormethazanone; 2-(p-Chlorophenyl)-tetrahydro-3-methyl-4H-1,3-thiazin-4-one 1,1-dioxide

Country	Effective Date	Description of action taken Grounds for decision
Saudi Arabia	June 1999	The Ministry of Health has withdrawn from the market products containing chlormezanone because of an unacceptable incidence of Stevens-Johnson syndrome. (Reference:

		Communication from the WHO Regional Office for the Eastern Mediterranean enclosing a notification from the Ministry of Health, Saudi Arabia, 20 June 1999.)
Singapore		The National Pharmaceutical Administration in the Ministry of Health has banned chlormezanone since it has been associated with reports of life-threatening toxic epidermal necrolysis and borderline major bullous forms. (Reference: Communication to WHO, 2 August 2000.)
South Africa	1998	The South African Medicines Control Council has withdrawn products containing chlormezanone because of the unacceptable risk-benefit profile which is not in the interest of public health. (Reference: Information from the Pharmaceutical Services in the Ministry of Health in South Africa.)
United Arab Emirates	1997	The Ministry of Health has withdrawn marketing approval for pharmaceutical products containing chlormezanone because it has been associated with an unacceptable incidence of Stevens-Johnson syndrome. (Reference: UAE Ministry of Health Drug Information Bulletin 1997 No. 3, p.2.)
Zimbabwe	1998	The Medicines Control Authority has cancelled the registration of all chlormezanone-containing products in the light of international actions taken on the basis of a safety evaluation of chlormezanone. This drug has been associated with an unacceptable incidence of Stevens-Johnson syndrome. (Reference: Drug Information Bulletin Vol.2, No.1, March 1998.)

Product name: **Cisapride**

CAS number: **810968-60-4**

Synonyms: Cisapridum; R-51619

Country	**Effective Date**	**Description of action taken Grounds for decision**
Armenia	July 2000	Cisapride has been voluntarily withdrawn because of the increased risk of cardiac arrhythmias in patients taking other medications or suffering from underlying conditions known to increase risk of cardiac arrhythmias. (Reference: Communication to WHO, 9 August 2000).
Brunei Darussalam	September 2000	The Drug Advisory Committee of the Ministry of Health has withdrawn cisapride (Prepulsid) from the market because of reports of serious cardiovascular adverse effects. (Reference: Official letter to WHO from Medical and Health Services Headquarters, Ministry of Health, Brunei Darussalam, 30 September 2000.)
Canada	7 August 2000	Health Canada has withdrawn cisapride because of the possibility of rare but serious heart complications including arrhythmias and sudden death. (Reference: Warnings Health

		Canada, 31 May 2000.)
Colombia	May 2000	The Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA) in Colombia, Colombian Ministry of Health has restricted the use of cisapride. It should be made available only if other therapeutic management is insufficient. (Reference: Letter from INVIMA to WHO, 21 August 2000.)
Germany	June 2000	The Federal Institute for Drugs and Medical Devices has suspended the marketing authorization of cisapride because of the association with cardiac arrhythmias and a number of deaths. (Reference: Communication to WHO, 3 July 2000.)
Ireland	September 1999	The Irish Medicines Board has restricted the indications for cisapirde following reports of cardiac arrhythmia, cardiac arrest and sudden death. (Reference: Irish Medicines Board, Drug Safety Newsletter.)
Japan	October 2000	The Ministry of Health and Welfare, Tokyo has decided to suspend marketing authorization of cisapride until its risk/benefit ratio is further reviewed. (Communication to WHO, 18 October 2000.)
Mauritius	July 2000	Cisapride was withdrawn from the market following reports of adverse cardiac events published by the FDA. (Reference: Letter to WHO from the Ministry of Health and Quality of Life, Port Louis, Mauritius, 27 December 2000.)
New Zealand		The Therapeutics section of the Ministry of Health, Wellington has severely restricted the use of cisapride in view of reports of cardiac arrhythmias associated with its use particularly in conjunction with erythromycin, clarithromycin, fluconazole, itraconazole or miconazole. (Reference: Prescriber Update No.14, February 1997.)
Oman	April 2000	The Directorate General of Pharmaceutical Affairs & Drug Control has suspended the marketing of cisapride because of the possibility of rare but serious heart complications including arrhythmias and sudden death. (Reference Circular No. 28/2000 Directorate General of Pharmaceutical Affairs, Ministry of Health, Sultanate of Oman, 30 April 2000.)
Philippines	2000	The Department of Health Bureau of Food and Drugs has banned the use of cisapride because of documented reports on adverse events including deaths associated with its use. (Reference: Administrative Order No.97 s 2000, 9 August 2000. Communication from the Department of Health and Bureau of Food and Drugs to WHO, 15 August 2000.)
United Arab Emirates	15 April 2000	Indications for use of cisapride have been severely restricted because of the risk of rare but serious cardiac events associated with the drug. (Reference: Communication with WHO, 10 July 2000.)
United Kingdom	July 2000	The Medicines Control Agency has withdrawn cisapride from the market because of rare but serious cardiac adverse effects. (Reference: Advice from the Medicines Control Agency, 21 July 2000.)
USA	April 2000	Cisapride has been voluntarily withdrawn from the market because of the risk of rare but serious cardiac events

		associated with the drug. These include heart rhythm disorders and deaths associated mostly with the use of the drug in people who are either taking certain other medications or who have certain underlying conditions that are known risk factors. (Reference: www.fda.gov/medwatch/safety/2000/propull.htm)

Product name: **Dantron**

CAS number: **117-10-2**

Synonyms: Danthron, Antrapurol, Chrysazin, Dianthon

Country	Effective Date	Description of action taken Grounds for decision
Canada	November 1997	After reviewing the benefits and risks associated with the use of dantron-containing stimulant laxatives, Health Canada has concluded that dantron is a genotoxic animal carcinogen and that the risks of using these products outweigh the therapeutic benefits. Dantron is a synthetic anthraquinone and, although there is no direct evidence that it has caused cancer in humans, it may have a carcinogenic potential. Manufacturers have voluntarily ceased sale of their products. (Reference: Press Release 1997-64, 25 November 1997.)
United Kingdom	May 2000	The Medicines Control Agency has severely restricted the use of the laxative, dantron following studies showing genotoxicity. It is now restricted to use in terminally ill adult patients only. (Reference: Communication to WHO, 30 August 2000 from the Medicines Control Agency, Department of Health, United Kingdom.)

Product name: **Dequalinium**

CAS number: **6707-58-0**

Synonyms: Decalinium chloride; decaminium

Country	Effective Date	Description of action taken Grounds for decision
Bulgaria	August 1998	The Bulgarian Drug Agency in the Ministry of Health withdrew the vaginal tablet of dequalinium (Efisol) because of serious adverse reactions reported in the country. (Ref: Communication to WHO from the Bulgarian Drug Agency, Ministry of Health, Bulgaria.)

Product name: **Dexfenfluramine hydrochloride**

CAS number: **3239-45-0**

Synonyms: (S)-N-Ethyl-α-methyl-3-trifluroromethylphenethylamine hydrochloride

Country	Effective Date	Description of action taken Grounds for decision
Lithuania	May 2000	The State medicines Control Agency has withdrawn for the market capsules of dexfenfluramine for reasons of safety. (Reference: Order of State Medicines Control Agency No. 8, 10 January 2000.) See also fenluramine.
Morocco	September 1997	The manufacturer of dexfenfluramine removed the product dexfenfluramine from the market because of the risk of rare, but potentially fatal pulmonary artery hypertension. (Reference: Letter from the Direction du médicament et de la pharmacie, Rabat, 8 September 2000.)
Philippines	September 1998	The Department of Health Bureau of Food and Drugs has noted the voluntary withdrawal by the sponsoring company of the anorectic drugs fenfluramine and dexfenfluramine. (Reference: Communication from the Department of Health and Bureau of Food and Drugs to WHO, 15 August 2000.)

Product name: **Diphenoxylate**

CAS number: **915-30-0**

Synonyms: Diphenoxylati hydrochloridium; R-1132

Country	Effective Date	Description of action taken Grounds for decision
Bahrain	2000	The Ministry of Health has restricted the prescription of medicines containing diphenoxylate as controlled medicines that should be dispensed only on special prescriptions issued by the Directorate of Pharmacy and Drug Control at the Ministry of Health with effect from 2 May 2000. (Reference: Communication with WHO, 27 June 2000.)

Product name: **Doxycycline hydrochloride (capsules)**

CAS number: **24390-14-5**

Synonyms: 2- naphtacenecarboxamide-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-

Country	Effective Date	Description of action taken Grounds for decision
Morocco	May 2000	The National Advisory Commission for Pharmacovigilance has suspended marketing authorization for all pharmaceutical products containing doxycycline in capsule form. There is evidence of a high risk of oesophageal damage with the administration of capsules of doxycycline. (Reference: Letter from the Direction du médicament et de la pharmacie, Rabat, 8 September 200

Product name: **Dronabinol**

CAS number: **1972-08-3**

Synonyms: NSC-134454

Country	Effective Date	Description of action taken Grounds for decision
USA	1998	Dronabinol is reclassified from Schedule II to Schedule III of the US Controlled Substances Act. Dronabinol is internationally controlled in Schedule II of the 1971 Convention on Pyschotropic Substances. (Reference: Federal Register 63(214): 59751-53 (1998).)

Product name: **Ebrotidine**

CAS number: **100981-43-9**

Synonyms: p-bromo-N-[(E)-({2-[{(2-[diaminomethylene)amino]-4-thiazoyl}methyl)thio]ethyl}amino)methylene]benzenesulfonamide

Country	Effective Date	Description of action taken Grounds for decision
Peru	October1998	La Direcciòn General de Medicamentos, Insumos y Drogas (DIGEMID) of the Ministry of Health withdrew marketing authorization for the histamine H_2 receptor antagonist ebrotidine(Ebrocit) because of reports of serious liver dysfunction particularly on long-term treatment and when the drug was administered with anti-inflammatory agents and corticosteroids. (Reference: Alerta DIGEMID No. 07-98, 12 October 1998).

Product name: **Epoetin alfa and epoetin beta**

CAS number: **113427-24-0 (alfa) 122312-54-3 (beta)**

Synonyms: Erythropoeitin

Country	Effective Date	Description of action taken Grounds for decision
Mauritius		The Ministry of Health and Quality of Life has restricted the use of injections of epoetin alfa and beta, recombinant erythropoeitins, used in the management of anaemia associates with chronic renal failure in patients requiring renal dialysis to use in hospitals and renal dialysis centres. This is in order to minimize the risk of abuse of the drug by athletes and for horse racing. (Reference: Letter to WHO from the Ministry of Health and Quality of Life, Port Louis, Mauritius, 27 December 2000.)

Product name: **Erythrityl tetranitrate**

CAS number: **7297-25-8**

Synonyms: Erythrol nitrate; Nitroerythrite; Nitroerythrol

Country	Effective Date	Description of action taken Grounds for decision
USA	1998	The Food and Drug Administration has withdrawn conditional approval of abbreviated new drug applications for single-entity drug products containing erythrityl tetranitrate because there is a lack of substantial evidence that these drugs are effective for indications relating to the management, prophylaxis or treatment of anginal attacks. (Reference: Federal Register 63(200): 55616-55617 (1998).)

Product name: **Fenfluramine**

CAS number: **458-24-2**

Synonyms: Benzeneethanamine, N-ethyl- -methyl-3-(trifluoromethyl)-, hydrochloride

Country	Effective Date	Description of action taken Grounds for decision
Philippines	September 1998	The Department of Health Bureau of Food and Drugs has noted the voluntary withdrawal by the sponsoring company of the anorectic drugs fenfluramine and dexfenfluramine. (Reference: Communication from the Department of Health and Bureau of Food and Drugs to WHO, 15 August 2000.)
United Arab Emirates	1997	The Ministry of Health has withdrawn the marketing approval for fenfluramine the only anorectic drug approved in the UAE. (Reference: UAE Ministry of Health Drug Information Bulletin 1997 No. 3, p.2.)

Product name: **Flunitrazepam**

CAS number: **1622-62-4**

Synonyms: 2h-1,4-benzodiazepin-2-one, 5-(2-fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-; 5-(o-fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2h-1,4-benzodiazepin-2-one

Country	Effective Date	Description of action taken Grounds for decision
South Africa	1999	The South African Medicines Control Council has withdrawn registration of all 2 mg formulations of flunitrazepam and has scheduled 1 mg tablets in Schedule 6 of the Narcotic Drugs Regulations. It has also decreed that all flunitrazepam-containing products be reformulated to include a bitter taste and colorant in order to minimize risk of illegal use in facilitating crimes. (Reference: Information from the Pharmaceutical Services in the Ministry of Health in South Africa.)

Product name: **Furazolidone**

CAS number: **67-45-8**

Synonyms: Nitrofurazolidonum

Country	Effective Date	Description of action taken Grounds for decision
Yemen	1998	The Supreme Board of Drugs and Medical Devices has withdrawn all formulations of the nitrofuran derivative, furazolidone, because many other safer and more effective alternatives are available. (Reference: Communications from WHO Representative, Yemen, 17 December and 10 October

		1998.)

Product name: **Gentamicin (topical preparations)**

CAS number: **1403-66-3**

Synonyms: O-3-Deoxy-4-C-methyl-3-(methylamino- -L-arabino-pyranosyl-(1 6)-O-[2,6,diamino-2,3,4,6-tetradeoxy- -D-erythro-hexopyranosyl-(1 4)]-2-deoxy-D-streptamine (gentamicin C_{1A})

Country	Effective Date	Description of action taken Grounds for decision
Armenia	July 2000	The Drug and Medical Technology Agency withdrew registration of gentamicin ointment for 'in situ' treatment of minor infections because antibiotics that are also available for systemic use are not considered acceptable for topical use because of resistance development. (Reference: Communication to WHO, 9 August 2000)

Product name: **Grepafloxacin hydrochloride**

CAS number: **161967-81-3**

Synonyms: OPC-17116

Country	Effective Date	Description of action taken Grounds for decision
Armenia	July 2000	Grepafloxacin has been voluntarily withdrawn after the observation of severe cardiovascular events among patients. (Reference: Communication to WHO, 9 August 2000.)
Lithuania	November 1999	Marketing authorization for grepafloxacin was suspended by the State Medicines Control Agency. (Reference: Order of State Medicines Control Agency No. 96, 15 November 1999.)
Peru	December 1999	La Direcciòn General de Medicamentos, Insumos y Drogas (DIGEMID) of the Ministry of Health has communicated to health professionals that Glaxo Wellcome has voluntarily withdrawn the fluoroquinolone grepafloxacin from the market because of prolongation of the QT interval giving rise to ventricular arrhythmias known as torsades de pointes. (Reference: Alerta DIGEMID No. 12-99, 15 December 1999).
Singapore		Grepafloxacin has been voluntarily withdrawn due to an effect of the drug on cardiac repolarization, manifested as QT interval prolongation. Some patients may be at risk of the very rare but serious ventricular arrhythmia known as torsades de pointes. (Reference: Communication to WHO, 2 August 2000.)

United Kingdom	October 1999	Grepafloxacin (Raxar) was voluntarily withdrawn from the market by the licence holder from the market because of a small number of severe cardiac arrhythmias among patients in post-marketing surveillance. (Ref: Communication to WHO 30 August 2000 from the Medicines Control Agency, Department of Health, United Kingdom.)

Product name: **Ginkgo biloba**

CAS number: **EGB-762**

Synonyms: Fossil Tree; GBE-761; Kew Tree; Maidenhair Tree

Country	Effective Date	Description of action taken Grounds for decision
Germany	1998	The Federal Institute for Drugs and Medical Devices has extended the suspension of parenteral infusion formulations after having received several reports of adverse reactions associated with its use, most of which described anaphylactic symptoms (shock, fever, leukocytosis, and cardiac arrhythmia), in some cases life-threatening. (Reference: Communication from the Federal Institute for Drugs and Medical Devices, 19 June 1998.)

Product name: **Ketamine hydrochloride**

CAS number: **1867-66-9**

Synonyms: CI-581; CN-52372-2; Ketamini Hydrochloridum

Country	Effective Date	Description of action taken Grounds for decision
Singapore		The National Pharmaceutical Administration in the Ministry of Health has rescheduled ketamine as a narcotic drug because of its high abuse potential. (Reference: Communication to WHO, 2 August 2000.)

Product name: **Ketorolac**

CAS number: **4103-06-3**

Synonyms: Ketorolac tromethamine; H-pyrrolizine-1-carboxylic acid, 5-benzoyl-2,3-dihydro, (+/-)-, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

Country	Effective Date	Description of action taken Grounds for decision
Jamaica	1998	The Ministry of Health, Standards and Regulation did not approve registration of the non-steroidal anti-inflammatory drug, ketorolac due to adverse effects. (Reference: Communication to WHO from The Ministry of Health, Standards and Regulation, Kingston, Jamaica 26 September 2000.)

Product name: **Lamivudine**

CAS number: **131086-21-0; 134678-17-4**

Synonyms: 3TC; (-)-2'Deoxy-3'-thiacytidine

Country	Effective Date	Description of action taken Grounds for decision
Singapore		The National Pharmaceutical Administration in the Ministry of Health has restricted the use of lamivudine for the treatment of chronic hepatitis B to gastroenterologists only. This decision has been taken because prolonged treatment may result in the emergence of resistant strains. Furthermore post-treatment hepatitis that can be fatal in patients with poor hepatic function or cirrhosis has been observed in patients after withdrawal of therapy. (Reference: Communication to WHO, 2 August 2000.)

Product name: **Levamisole hydrochloride**

CAS number: **16595-80-5**

Synonyms: Levamisoli hydrochloridum; l-tetramisole hydrochloride

Country	Effective Date	Description of action taken Grounds for decision
Viet Nam	April 2000	The Drug Administration of Viet Nam in the Ministry of Health has withdrawn the registration of products with the anthelminthic, levamisole as the active ingredient. The reason for withdrawal is that these products have adverse effects that cause encephalitis and mortality. (Reference: Directive from Ministry of Health, Drug Administration of Viet Nam, No. 13/2000/QD-QLD, 27 April 2000.)

Product name: **Lexipafant**

CAS number: **139133-26-9**

Synonyms: Ethyl-N-methyl-N-[α-(2-methylimidazole[4,5-c]pyridin-1-yl)tosyl]-L-leucinate

Country	Effective Date	Description of action taken Grounds for decision
EMEA	May 1998	The European Agency for the Evaluation of Medicinal Products (EMEA) has refused marketing authorization for lexipafant. The Committee for Proprietary Medicinal Products reviewed the data submitted by the company and considered that lexipafant was not approvable for the treatment of severe acute pancreatitis on the basis of the submitted data. (Reference: EMEA Press Release, London, 5 May 1998.)

Product name: **Loxoprofen sodium**

CAS number: **68767-14-6**

Synonyms: p-[(2-oxocyclopentyl)methyl]hydratropate dihydrate

Country	Effective Date	Description of action taken Grounds for decision
Singapore		The National Pharmaceutical Administration in the Ministry of Health has not approved loxoprofen sodium because of reports of colonic ulceration and death associated with its use. (Reference: Communication to WHO, 2 August 2000.)

Product name: **Medifoxamine**

CAS number: **32359-34-5**

Synonyms: NN-Dimethyl-2,2-diphenoxyethylamine

Country	Effective Date	Description of action taken Grounds for decision
France	July 1999 suspended, March 2000	The Medicines Agency has announced the withdrawal of the antidepressant, medifoxamine from the market after a pharmacovigilance enquiry performed in France revealed

	withdrawn	evidence of hepatic injury associated with the use of medifoxamine. (Reference: Infofax Pharmacovigilance, Agence du Médicament, Saint-Denis, 30 June 1999.)
Morocco	June 1999	The manufacturer has withdrawn medifoxamine from the market because of evidence of hepatic injury. (Reference: Letter from the Direction du médicament et de la pharmacie, Rabat, 8 September 2000.)

Product name: **Mepacrine**

CAS number: **83-889-6**

Synonyms: Arrithinum; Antimalarinae Chlorhydras; Chinacrina Mepacrini Hydrochloridium; Quinacrine Hydrochloride

Country	Effective Date	Description of action taken Grounds for decision
India	August 1998	The Government has issued a notification banning the import, manufacture, sale and distribution of mepacrine (quinacrine) for use as a contraceptive or sterilisation agent. Penalties include up to three years imprisonment and fines of up to Rs. 5,000. This action has been taken following clinical trials undertaken by the Indian Council of Medical Research that raised questions about the safety of the drug. (Reference: The Hindu. Use of quinacrine as contraceptive banned, 18 August 1998.)

Product name: **Metamizole sodium**

CAS number: **68-89-3**

Synonyms: Dipyrone; Noramidopyrine methanesulfonate sodium; Methanesulfonic acid,[(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl) methylamino]-, sodium salt

Country	Effective Date	Description of action taken Grounds for decision
Armenia	February 2000	The Drug and Medical Technology Agency has suspended the marketing authorization of metamizole sodium (tablets and solution). The decision is based on a large number of reports on agranulocytosis in Sweden since 1996 and other dangerous adverse effects. (Reference: Communication to WHO, 9 August 2000.)
Colombia	June 2000	The Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA) in Colombia, Colombian Ministry of Health has restricted the use of metamizole either alone or in

		combination. These products should be available only if other therapeutic management is insufficient. (Reference: Resolucion No. 259048, INVIMA, 22 June 2000, Ministerio de Salud.)
Morocco	May 2000	The Minister of Public Health has decided to suspend the marketing authorization for products containing metamizole sodium on the recommendation of the National Advisory Commission for Pharmacovigilance. This recommendation followed an official survey which showed severe adverse reactions associated with this product. (Reference: Letter from the Direction du médicament et de la pharmacie, Rabat, 8 September 2000.)
Sweden	1999	The Medical Products Agency has suspended the marketing authorization for metamizole sodium with effect from 28 April 1999. The decision is based on a larger than expected number of reports of agranulocytosis in Sweden since 1996 (1 in 1,700). (References: EU/EEA Rapid Alert, Läkemedelsverket (Medical Products Agency), 28 April 1999.)
Syria	1998	The Suprim Technical Committee and the Ministry of Health has instructed all local drug factories to stop manufacturing metamizole sodium (dipyrone) ampoules with immediate effect. (Reference: Announcement from the Directorate No: 1784 dated 2/2/98.)
Yemen	1998	The Supreme Board of Drugs and Medical Appliances has withdrawn all formulations of metamizole sodium because of its potential to cause anaphylactic shock and agranulocytosis. (Reference: Communications from WHO Representative, Yemen, 17 December and 10 October 1998.)
Zimbabwe	1998	The Medicines Control Authority has cancelled the registration of all metamizole sodium (dipyrone)- containing products due to the potential risk of metamizole sodium causing fatal agranulocytosis. (Reference: Drug Information Bulletin Vol.2, No.1, March 1998.)

Product name: **Methylrosanilinium chloride**

CAS number: **548-62-9**

Synonyms: Crystal violet; Cl Basic violet; Gentian violet; Methylrosaniline chloride

Country	Effective Date	Description of action taken Grounds for decision
Malaysia	April 1998	The Drug Control Authority decided to cancel the registration of all existing products containing methylrosanilinium chloride following reports of adverse reactions and toxicity such as buccal ulceration, stomatitis, kerato-conjunctivitis, irritation and sensitivity reactions encountered with the use of products containing this dye. Studies have shown methylrosanilinium chloride to be a carcinogen in mice and it has been labelled as a mutagen, a mitotic poison and a clastogen. (Reference:

		Berita Ubat-Ubatan Vol.12, No.2, August 1998.)

Product name: **Metoclopramide (paediatric)**

CAS number: **364-62-5**

Synonyms: AHR-3070-C; Metoclopramidi Hydrochloridium

Country	Effective Date	Description of action taken Grounds for decision
Syria	1999	The Suprim Technical Committee and the Ministry of Health has prohibited the use of metoclopramide in children less than 20 kg of weight because of reports of sensitivity reactions. . (Reference: Announcement from the Directorate No: 5615/3/15, 1999.)

Product name: **Mibefradil**

CAS number: **116644-53-2**

Synonyms: (1S,2S)-(2-{[3-(2-Benzinidazoylyl)propyl]methylamine}-ethyl-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride

Country	Effective Date	Description of action taken Grounds for decision
Armenia	July 2000	Mibefradil has been voluntarily withdrawn on the basis of a large number of reports of life-threatening interactions of the drug: extremely low heart rates and a risk of muscle injury. (Reference: Communication to WHO, 9 August 2000.)
Bulgaria	April 1999	The Bulgarian Drug Agency in the Ministry of Health withdrew the calcium channel blocking agent, mibefradil (Posicor) because of serious adverse reactions worldwide. (Reference: Communication to WHO from the Bulgarian Drug Agency, Ministry of Health, Bulgaria.)
Germany	August 1998	The Federal Institute for Drugs and Medical Devices has suspended the marketing authorization for mibefradil because it considers that mibefradil has a negative benefit/risk ratio. In particular, it has a life-threatening potential to induce cardiac arrhythmias (including torsades de pointes) especially when taken concomitantly with other medications. (Reference: Communication from the Federal Institute for Drugs and Medical Devices, 21 August 1998.)
Jamaica	February 1998	The calcium channel blocking agent, mibefradil was voluntarily withdrawn from the market by Hoffman La Roche. (Reference: Communication to WHO from The Ministry of Health,

		Standards and Regulation, Kingston, Jamaica, 26 September 2000.)
Peru	1998	La Direcciòn General de Medicamentos, Insumos y Drogas (DIGEMID) of the Ministry of Health withdrew marketing authorization for mibefradil (Posicor) following reports of serious adverse effects caused by the interaction with other medicines. (Reference: Alerta DIGEMID No. 04-98, 1998.)
South Africa	1998	The South African Medicines Control Council has withdrawn products containing mibefradil because of safety concerns in relation to potential for serious drug interactions. (Reference: Information from the Pharmaceutical Services in the Ministry of Health in South Africa.
United Kingdom	July 1998	Mibefradil was voluntarily withdrawn from the market by the manufacturer worldwide due to an increasing number of reports of serious interactions with a wide range of drugs. . (Reference: Communication to WHO, 30 August 2000 from the Medicines Control Agency, Department of Health, United Kingdom.)
USA	1998	Roche laboratories announced the voluntary market withdrawal of the antihypertensive and antianginal medication mibefradil (Posicor). This action was taken because of information on a number of drug interactions, some of them serious that occur when mibefradil is taken together with other medications. (Reference: Dear Doctor letter of June 8 1998. www.fda.gov/medwatch/safety/1998.)

Product name: **Misoprostol**

CAS number: **59122-46-2**

Synonyms: SC-29333. Methyl 7-{1R,2R,3R)-3-hydroxy-2-[(E)-(4RS)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl}heptanoate

Country	Effective Date	Description of action taken Grounds for decision
Oman	April 2000	The Directorate General of Pharmaceutical Affairs & Drug Control has rescheduled misoprostol as a non-psychotropic restricted controlled item because of international data concerning its potential abuse and risk of dependence. (Reference Circular No. 25/2000 Directorate General of Pharmaceutical Affairs, Ministry of Health, Sultanate of Oman, 25 April 2000.)

Product name: **Nandrolone**

CAS number: **360-70-3**

Synonyms: ESTR-4-EN-3-ONE, 17-[(1-oxodecyl)oxy]-,(17beta); nortesterone decyclate

Country	Effective Date	Description of action taken Grounds for decision
France	April 1998	The Medicines Agency has withdrawn from the market all injectable formulations of the anabolic steroid, following a routine re-evaluation of the benefit/risk ratio showing a lack of clinical data to support the efficacy of the product in the claimed indication (confirmed osteoporosis in postmenopausal women. (Reference: Communication from the Agence du Médicament, 3 April 1998.)

Product name: **Oxeladin citrate**

CAS number: **52432-72-1**

Synonyms: 2-(2-Diethylaminoethoxy)ethyl 2 ethyl-2-phenylbutarate dihydrogen citrate

Country	Effective Date	Description of action taken Grounds for decision
Armenia	July 2000	The Drug and Medical Technology Agency rejected the registration of oxeladin since studies in Germany have shown potential carcinogenicity of the drug. (Reference: Communication to WHO, 9 August 2000.)

Product name: **Pexiganan**

CAS number:

Synonyms:

Country	Effective Date	Description of action taken Grounds for decision
USA	March 2000	The Food and Drug Administration has not approved marketing of the topical anti-infective agent pexiganan acetate on the grounds that efficacy has not been sufficiently demonstrated. (Reference: The US FDA's Anti-infective Drugs Advisory Committee, 4 March 2000.)

Product name: **Phenolphthalein**

CAS number: **77-09-8**

Synonyms: 3,3-bis-(p-hydroxyphenyl)phthalide; 3,3-bis(4-hydroxyphenyl)-1(3H)-isobenzofuranone; 3,3-bis(4-hydrophenyl)-phthalide

Country	Effective Date	Description of action taken Grounds for decision
Canada	September 1997	After reviewing the benefits and risks associated with the use of phenolphthalein-containing laxatives Health Canada has concluded that there is a risk that phenolphthalein may cause cancer in humans, therefore the authority to sell and distribute these products has been revoked. (Press Release 1997-54, 30 September 1997.)
Morocco	November 1997	The Direction du médicament et de la pharmacie has suspended marketing authorization for phenolphthalein. (Reference: Letter from the Direction du médicament et de la pharmacie, Rabat, 8 September 2000.)
Oman	1998	The Directorate General of Pharmaceutical Affairs & Drug Control has prohibited the registration, import and sale of phenolphthalein in all laxative preparations, including candies or chewing gum, because of a potential risk of carcinogenicity. (Reference: Pharmaceutical Newsletter 5(4): 8 (1997), Ministry of Health, Muscat.)
Saudi Arabia	June 1999	The Ministry of Health has withdrawn from the market laxative products containing phenolphthalein because of a potential risk of carcinogenicity. (Reference: Communication from the WHO Regional Office for the Eastern Mediterranean enclosing a notification from the Ministry of Health, Saudi Arabia, 20 June 1999.)
Singapore		The National Pharmaceutical Administration in the Ministry of Health has rescheduled phenolphthalein to a Prescription-Only-Medicine due to its genotoxic and carcinogenic potential. (Reference: Communication to WHO, 2 August 2000.)

Product name: **Phentermine**

CAS number: **122-09-8**

Synonyms: α,α-Dimethylphenethylamin

Country	Effective Date	Description of action taken Grounds for decision
United Kingdom	April 2000	The Medicines Control Agency has banned the anorectic agent, phentermine on the basis of a European Commission decision stating that risks outweigh the benefits. (Ref: Communication to WHO, 30 August 2000 from the Medicines Control Agency, Department of Health, United Kingdom.)

Product name: **Phentolamine mesilate**

CAS number: **65-28-1**

Synonyms: Phentolamine Methanesulphonate; Phentolamini Mesilas. 3-[N-(2-Imidazolin-2-ylmethyl)-p-toluidino]phenol methanesulphonate

Country	Effective Date	Description of action taken Grounds for decision
Singapore		The National Pharmaceutical Administration in the Ministry of Health has not approved phentolamine mesylate, a drug used for the treatment of erectile dysfunction because of abnormal findings in rat carcinogenicity studies. (Reference: Communication to WHO, 2 August 2000.)

Product name: **Phenylbutazone**

CAS number: **50-33-9**

Synonyms: Butadione; 3,5-pyrazolidinedione, 4-butyl-1,2-diphenyl-4-butyl-1,2-diphenyyl-3,5,pyrazolidinedione

Country	Effective Date	Description of action taken Grounds for decision
Armenia	February 2000	The Drug and Medical Technology Agency has suspended the marketing authorization of phenylbutazone for oral, parenteral and topical use because of its toxicity. (Reference: Communication to WHO, 9 August 2000.)

Product name: **Piperazine**

CAS number: **110-85-0**

Synonyms: Butadione; 3,5-pyrazolidinedione, 4-butyl-1,2-diphenyl-4-butyl-1,2-diphenyyl-3,5,pyrazolidinedione

Country	Effective Date	Description of action taken Grounds for decision
Armenia	July 2000	The Drug and Medical Technology Agency withdrew registration of the anthelminthic product, piperazine because of reports of questionable safety with detection of neurotoxicity, hypersensitivity and nitrosamine-generating ability. (Reference: Communication to WHO, 9 August 2000.)

Product name: **Promethazine**

CAS number: **60-87-7**

Synonyms: 10-[2-(Dimethylamino)propyl]-phenothiazine; 10H-Phenothiazine-10-ethanamine, N,N,alpha-trimethyl-.

Country	Effective Date	Description of action taken Grounds for decision
Morocco	May 2000	The National Commission form Pharmacovigilance has restricted the administration of this product for children over 2 years of age. (Reference: Letter from the Direction du médicament et de la pharmacie, Rabat, 8 September 2000.)

Product name: **Proxibarbal**

CAS number: **2537-29-3**

Synonyms: Proxibarbital

Country	Effective Date	Description of action taken Grounds for decision
France	April 1998	The Medicines Agency has withdrawn proxibarbal from the market after a benefit/risk evaluation showed that it may induce immunoallergic thrombocytopenia with potentially severe consequences. Proxibarbal was indicated for the treatment of minor signs of anxiety and hot flushes of the menopause and migraine. The company has already withdrawn proxibarbal in Italy, Spain, Portugal and Turkey. It is still marketed in Hungary and Poland. (Reference: Communication from the Agence du Médicament, 16 April 1998.)

Product name: **Pyrithione zinc**

CAS number: **13463-41-7**

Synonyms: Zinc 2-Pyridinethiol 1-oxide; zinc pyridinethione, Skin-ca

Country	Effective Date	Description of action taken Grounds for decision
Armenia	August 1999	The Drug and Medical Technology Agency has restricted the indications for pyrithione zinc to seborrhoeic dermatitis. (Reference: Communication to WHO, 9 August 2000.)
United Arab Emirates	1997	The Ministry of Health has withdrawn the marketing approval for pyrithione zinc that is indicated for the treatment of dandruff or psoriasis. This follows concern raised by the FDA and Canada after closer analysis of the product revealed that it contained an (unlabelled) prescription strength corticosteroid (clobetasol). (Reference: UAE Ministry of Health Drug Information Bulletin, No. 3, p.2, 1997.)

Product name: **Pumactant**

CAS number:

Synonyms: Artificial Lung Expanding Compound

Country	Effective Date	Description of action taken Grounds for decision
United Kingdom	April 2000	Pumactant was voluntarily withdrawn from the market by the licence holder following the results of a randomized clinical trial which showed unexpectedly higher mortality rate in neonates given pumactant. (Reference: Communication to WHO, 30 August 2000 from the Medicines Control Agency, Department of Health, United Kingdom.)

Product name: **Rituximab**

CAS number: **174722-31-7**

Synonyms: IDEC-102

Country	Effective Date	Description of action taken Grounds for decision
United Kingdom	February 1999	The Medicines Control Agency has severely restricted the use of the monoclonal antibody used in the treatment of non-Hodgkin's lymphoma. Treatment should now only be undertaken in a hospital environment under the close supervision of a specialist oncologist/haematologist who has access to full resuscitation facilities. This is because of a number of cases of serious infusion-related reactions reported worldwide including 8 with a fatal outcome. (Reference: Communication to WHO, 30 August 2000 from the Medicines Control Agency, Department of Health, United Kingdom.)

Product name: **Sertindole**

CAS number: **106516-24-9**

Synonyms: Lu-23-174; 1-(2-{4-[5-chloro-1-(p-fluorophenyl)indol-3-yl]piperidine}ethyl)2-imidazolidinone

Country	Effective Date	Description of action taken Grounds for decision
Bulgaria		The Bulgarian Drug Agency in the Ministry of Health withdrew the atypical antipsychotic agent sertindole (serdolect) because of serious adverse reactions worldwide. (Reference: Communication to WHO from the Bulgarian Drug Agency, Ministry of Health, Bulgaria.)
United Kingdom	December 1998	The manufacturer of the antipsychotic medication, sertindole (serdolect) voluntarily suspended the availability of serdolect. This is because of concerns about reports of cardiac arrhythmias and sudden cardiac death associated with its use. (Reference: Message from Committee on Safety of Medicines, 2 December 1998.)

Product name: **Sibutramine**

CAS number: **106650-56-0**

Synonyms: BTS-54524 (sibutamine hydrochloride)

Country	Effective Date	Description of action taken Grounds for decision
USA	1998	The Drug Enforcement Administration has placed sibutramine

		for the management of obesity, in Schedule IV of the Controlled Substances Act. This scheduling is based on the low potential for abuse of sibutramine and the fact that it has a currently accepted medical use in treatment in the United States. (Reference: Federal Register 63(28): 6862 (1998).)

Product name: **Sulfaguanidine**

CAS number: **57-67-0**

Synonyms: Sulgin. Solfaguanidina

Country	Effective Date	Description of action taken Grounds for decision
Armenia	July 2000	The Drug and Medical Technology Agency withdrew registration of the antidiarrhoeal drug sulgin because of increasing resistance to sulfonamides and also because nonabsorbable sulfonamides containing antidiarrhoeal products are not recommended in the treatment of diarrhoea. (Reference: Communication to WHO, 9 August 2000.)

Product name: **Terfenadine**

CAS number: **50679-08-8**

Synonyms: 1-Piperidinebutanol; α-[4-(1,1-dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol

Country	Effective Date	Description of action taken Grounds for decision
France	1999	The Agence du Médicament has withdrawn the antihistamine, terfenadine from the market because the risk of ventricular arrhythmias does not justify the continuation of terfenadine on the market. (Reference: Décision de la Commission des communautés européennes du 22 September 1998.)
Iceland	January 1999	The State Committee on Pharmaceuticals in Iceland withdrew the marketing authorization for 120 mg tablets of terfenadine and 60 mg tablets were switched from OTC to POM status in January 1998 due to the occurrence of serious adverse effects. (Reference: Communication to WHO from the State Committee on Pharmaceuticals in Iceland, 17 October 2000.)
Mauritius	December 1998	The Ministry of Health and Quality of Life has withdrawn terfenadine from the market following reports of fatal drug interactions with commonly use drugs. . (Reference: Letter to WHO from the Ministry of Health and Quality of Life, Port Louis, Mauritius, 27 December 2000.)

Morocco	February 1997	The National Advisory Commission for Pharmacovigilance has reviewed the overall risk-benefit of terfenadine and decided to withdraw terfenadine from the market because of the risk of cardiac arrhythmia associated with the administration of terfenadine. (Reference: Letter from the Directorate of Medicines and Pharmacy, Rabat, 24 August 1999.)
Oman	1997	The Directorate General of Pharmaceutical Affairs & Drug Control has prohibited the registration, import and sale of terfenadine due to reported serious cardiac adverse effects associated with its inappropriate use. (Reference: Pharmaceutical Newsletter 5(4): 8 (1997), Ministry of Health, Muscat.)
Saudi Arabia	June 1999	The Ministry of Health has withdrawn from the market products containing the histamine H1-receptor antagonist, terfenadine, because of reports of a potentially fatal heart condition associated with its use. (Reference: Communication from the WHO Regional Office for the Eastern Mediterranean enclosing a notification from the Ministry of Health, Saudi Arabia, 20 June 1999.)
Singapore		The National Pharmaceutical Administration in the Ministry of Health has banned terfenadine because of its association with rare but serious heart problems when taken with certain drugs, including antibiotics and antifungal drugs. (Reference: Communication to WHO, 2 August 2000.)
USA	1998	Hoechst, Marion Roussel and Baker Norton Pharmaceuticals have voluntarily discontinued distribution and marketing of all terfenadine-containing antihistamine products in the United States. Terfenadine-containing products have been associated with rare, but serious heart problems when taken with certain antibiotics and antifungals. The FDA reminded consumers and health care providers that equally safe and effective alternative drugs are available. (Reference: FDA Talk Paper www.fda.gov/bbs/topics/ANSWERS/ANS00853. html)

Product name: **Tianeptine sodium**

CAS number: **66981-73-5**

Synonyms: tianeptine. 7-[(3-chloro-6,11–dihydro-6-methyldibenzo[c,f][1,2] thiazepin-11-yl)amino]heptanoic acid S,S dioxide

Country	Effective Date	Description of action taken Grounds for decision
Singapore		The National Pharmaceutical Administration in the Ministry of Health has restricted the use of tianeptine sodium to psychiatrists due to its abuse potential. (Reference: Communication to WHO, 2 August 2000.)

Product name: **Tilbroquinol**

CAS number: **7175-09-9**

Synonyms: 7-Bromo-5-methyl-8-quinolinol

Country	Effective Date	Description of action taken Grounds for decision
France	1999	The Agence du Médicament has withdrawn the antiprotozoal, tilbroquinol from the market because the hepatoxicity of the drug outweighs the potential benefit. (Reference: Décision de retrait de l'autorisation de mise sur le marché d'Intetrix P granulés, du 5 juillet 1999.)
Morocco	November 1997	The Direction du médicament et de la pharmacie has suspended marketing authorization for the paediatric formulation of tilbroquinol and the therapeutic indications for the adult formulation were restricted to the treatment of intestinal amoebiasis. (Reference: Letter from the Direction du médicament et de la pharmacie, Rabat, 8 September 2000.)
Saudi Arabia	June 1999	The Ministry of Health has withdrawn from the market products containing tilbroquinol and a combination product containing tilbroquinol/tiliquinol because of a risk of hepatotoxicity associated with their use. (Reference: Communication from the WHO Regional Office for the Eastern Mediterranean enclosing a notification from the Ministry of Health, Saudi Arabia, 20 June 1999.)

Product name: **Tolcapone**

CAS number: **134308-13-7**

Synonyms: 3,4-Dihydroxy-4'-methyl-5 nitrobenzophenone; 3,4-Dihydroxy-5-nitrophenyl (4-methylphenyl)metahanone

Country	Effective Date	Description of action taken Grounds for decision
Australia	February 1999	Following overseas reports of serious and unpredictable hepatotoxicity associated with the use of the catechol-O-methyl transferase inhibitor, tolcapone (TamarR), including 3 fatalities, its registration has been withdrawn in Australia. (Reference: Australian Adverse Drug Reactions Bulletin Vol.18, No.1, February 1999.)
Bulgaria	April 1999	The Bulgarian Drug Agency in the Ministry of Health withdrew the antiparkisonism agent, tolcapone because of serious adverse reactions worldwide. (Ref: Communication to WHO

		from the Bulgarian Drug Agency, Ministry of Health, Bulgaria.)
EMEA	November 1998	The European Agency for the Evaluation of Medicinal Products has recommended the suspension of the marketing authorization for tolcapone. This follows several reports of severe and unpredictable hepatic reactions including fatal fulminant hepatitis. (Reference: Press release from the European Agency for the Evaluation of Medicines. 17 November 1998.)
Iceland	November 1998	The State Committee on Pharmaceuticals in Iceland withdrew the marketing authorization for tolcapone due to serious adverse effects. Since then the product has been available to specialist neurologists for the treatment of severe cases of Parkinson’s disease. (Reference: Communication to WHO from the State Committee on Pharmaceuticals in Iceland, 17 October 2000.)
Lithuania	December 1998	The State Medicines Control Agency has withdrawn from the market tablets of tolcapone. (Reference: Order of State Medicines Control Agency No. 123, 15 December 1998.)
Singapore		The National Pharmaceutical Administration in the Ministry of Health has restricted the use of tolcapone to neurologists as there are concerns over reports of severe hepatotoxicity associated with the use of the drug. (Reference: Communication to WHO, 2 August 2000.)
United Kingdom	November 1998	The manufacturer of the antiparkinsonism drug, tolcapone has voluntarily withdrawn it from the market. This follows a review of the hepatotoxic effects by the European Committee for Proprietary Medicinal Products (CPMP) which found that the overall balance of risks and benefit was no longer favourable. . (Reference: Communication to WHO, 30 August 2000 from the Medicines Control Agency, Department of Health, United Kingdom.)

Product name: **Tramadol**

CAS number: **27203-92-5**

Synonyms: CG-315

Country	Effective Date	Description of action taken Grounds for decision
Bahrain	2000	The Ministry of Health has restricted the prescription of medicines containing tramadol as controlled medicines that should be dispensed only on special prescriptions issued by the Directorate of Pharmacy and Drug Control at the Ministry of Health with effect from 2 May 2000. (Reference: Communication to WHO, 27 June 2000.)
Mauritius	October 2000	The Ministry of Health and Quality of Life has moved the product tramadol from Prescription-only status to Psychotropic in Schedule III of the New Dangerous Drugs Act based on

		1988 Convention Classification. This is because of widespread abuse resulting from unsupervised sales in pharmacies. (Reference: Letter to WHO from the Ministry of Health and Quality of Life, Port Louis, Mauritius, 27 December 2000.)

Product name: **Troglitazone**

CAS number: **97322-87-7**

Synonyms: 2,4-Thiazolidinedione, 5-[[4-[3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-benzopyran-2-yl)methoxy]-phenyl]methyl]-; (±)-all-rac-5-[p-[(6-Hydroxy-2,5,7,8-tetra-methyl-2-chromanyl)methoxy]benzyl]-2,4-thiazolidinedione

Country	Effective Date	Description of action taken Grounds for decision
Jamaica	2 February 1998	The Ministry of Health, Standards and Regulation did not approve registration of the antidiabetic agent troglitazone (Rezulin) due its hepatotoxicity. (Reference: Communication to WHO from The Ministry of Health, Standards and Regulation, Kingston, Jamaica 26 September 2000.)
Peru	May 2000	La Direcciòn General de Medicamentos, Insumos y Drogas (DIGEMID) of the Ministry of Health has communicated to health professionals that Warner Lambert Peru S.A. has voluntarily withdrawn the antidiabetic agent troglitazone from the market because of severe hepatic adverse effects associated with the use of this medicine. (Reference: Alerta DIGEMID No. 6 – 2000, 26 May 2000.)
USA	June 1999	The FDA and the manufacturer of troglitazone (RezulinR: Parke-Davis) - a drug used to treat type 2 diabetes mellitus (non-insulin dependent diabetes mellitus, or adult onset diabetes) has notified significant new changes to the labelling and recommended uses for this product. These changes are being made because new safety information (i.e., further evidence of serious and sometimes fatal liver injury in patients treated with troglitazone) indicates that its use should be limited to patients not adequately controlled by other therapy and should not be used as initial single agent therapy in the treatment of type 2 diabetes. The labelling changes also include recommendations for more extensive monitoring of liver function in patients using troglitazone. (Reference: FDA Talk Paper T99-28, 16 June 1999.)

Product name: **Trovafloxacin mesilate**

CAS number: **147059-72-1**

Synonyms: Trovafloxacin mesylate; CP-99219-27

Country	Effective Date	Description of action taken Grounds for decision
EMEA	May 1999	The European Agency for the Evaluation of Medicinal Products (EMEA) has recommended that marketing authorization for products containing trovafloxacin or alatrofloxacin be suspended. This follows reports of serious adverse hepatic events. (Reference: Public statement no. EMEA/17438/99, May 1999.)
Morocco	June 1999	The National Advisory Commission for Pharmacovigilance has decided to restrict the use of trovafloxacin and alatrofloxacin only to university hospitals under professional control and after a total examination of hepatic function. In the meantime, the Commission has launched a survey among prescribers in order to evaluate the risk/benefit balance of this product. (Reference: Letter from the Directorate of Medicines and Pharmacy, Rabat, 24 August 1999.)
Philippines	January 2000	The Department of Health Bureau of Food and Drugs have banned and withdrawn trovafloxacin since it is associated with hepatic adverse reactions. (Reference: Administrative order No. 1, s. 2000, 3 January 2000. Communication from the Department of Health and Bureau of Food and Drugs to WHO.
Singapore		The National Pharmaceutical Administration in the Ministry of Health has not approved trovafloxacin since it is associated with hepatic adverse reactions. (Reference: Communication to WHO, 2 August 2000.)
Spain	June 1999	The Spanish Medicines Agency has suspended the use of medicinal products contain the fluoroquinolone antibiotic, trovafloxacin and the intravenous formulation of the drug, alatrofloxacin (Reference: Communication from the Agencia Española de Medicamento, Ministerio de Sanidad y Consumo, Madrid, 15 June 1999. (Reference: Communication from the Agencia Española de Medicamento, Ministerio de Sanidad y Consumo, Madrid, 15 June 1999.)
Syria	1999	The Suprim Technical Committee and the Ministry of Health has withdrawn the licensing approval for trovafloxacin and cancelled it from the national essential drug list. (Reference: Announcement from the Directorate No: 1989/4/2 dated 2/9/99.)
USA	June 1999	The Food and Drug Administration has restricted the indications for products containing trovafloxacin or alatrofloxacin to patients having nosocomial infections or complicated intra-abdominal infections that are serious or life-threatening. This is due to concerns over the risks of serious liver toxicity. (Reference: FDA Talk Paper T99-26, June 1999.)
Viet Nam	July 1999	The Drug Administration of Viet Nam in the Ministry of Health has not approved the registration of trovafloxacin (Trovan) solution for injection 5 mg/ml and tablet 200 mg on the basis that these products have a potential for hepatotoxicity. (Reference: Directive from Ministry of Health, Drug Administration of Viet Nam, No. 2785/QLD, 15 July 1999.)

Product name: **Zopiclone**

CAS number: **43200-80-2**

Synonyms: 27267-RP; Zopiclonum

Country	Effective Date	Description of action taken Grounds for decision
Mauritius	May 2000	The Ministry of Health and Quality of Life has rescheduled the antipsychotic agent zopiclone into Schedule III of the consolidated Dangerous Drugs Act 2000 following observations of irrational use and emerging abuse. (Reference: Letter to WHO from the Ministry of Health and Quality of Life, Port Louis, Mauritius, 27 December 2000.)

Product name: **Combination barbiturate product**

Country	Effective Date	Description of action taken Grounds for decision
Saudi Arabia	June 1999	The Ministry of Health has withdrawn from the market a fixed combination barbiturate product containing phenobarbital, febarbamate and difebarbamate because of reports of hepatotoxicity. (Reference: Communication from the WHO Regional Office for the Eastern Mediterranean enclosing a notification from the Ministry of Health, Saudi Arabia, 20 June 1999.)

Product name: **Barbiturates in asthma preparations**

Country	Effective Date	Description of action taken Grounds for decision
South Africa	1998	The South African Medicines Control Council has withdrawn asthmatic preparations containing barbiturates because of the unacceptable risk-benefit profile which is not in the interest of public health. (Reference: Information from the Pharmaceutical Services in the Ministry of Health in South Africa.)

Product name: **Clopamide, reserpine and dihydroergocristine mesilate**

Country	Effective Date	Description of action taken Grounds for decision
Lithuania	May 2000	The State Medicines Control Agency has not renewed marketing authorization for combination products containing clopamide, reserpine and dihydroergocristine mesilate on the grounds that safer and more effective medicinal products are available. (Reference: Order of State Medicines Control Agency No. 61, 17 May 2000.)

Product name: **Kaolin and pectin**

Country	Effective Date	Description of action taken Grounds for decision
Yemen	1998	The Supreme Board of Drugs and Medical Devices has withdrawn the suspension formulation of the kaolin and pectin

because of a lack of evidence of efficacy in the management of diarrhoea. (Reference: Communications from WHO Representative, Yemen, 17 December and 10 October 1998.)

Product name: **Loratadine and pseudoephedrine**

Country	Effective Date	Description of action taken Grounds for decision
Philippines	2000	The Department of Health Bureau of Food and Drugs has banned and withdrawn the fixed-dose combination, loratadine + pseudoephedrine. (Reference: Administrative Order N0. 99 s. 2000, 9 August 2000. Communication from the Department of Health and Bureau of Food and Drugs to WHO, 15 August 2000.)

Product name: **Metamizole sodium, fenpiverinium bromide and pitofenone hydrochloride**

Country	Effective Date	Description of action taken Grounds for decision
Lithuania	May 2000	The State Medicines Control Agency has not renewed marketing authorization for combination products of metamizole sodium, fenpiverinium bromide and pitofenone hydrochloride for reasons of safety. (Reference: Decision of Drug Registration Bureau of SMCA. Minutes No.8 Draft of the Order of SMCA, 22 September 2000.)

Product name: **Pseudoephedrine and phenylpropanolamine**

CAS number: **90-82-4**

Synonyms: *d*-Isoephedrine.d-? -Ephedrine

Country	Effective Date	Description of action taken Grounds for decision
Morocco	August 1999	The Commission for Pharmacovigilance in Morocco decided to restrict the use of all drug products containing pseudoephedrine or phenylpropanolamine to adults and has prohibited their use in children under 12 years. The products have also been subjected to prescription control. This decision was taken following reports of serious risks to health associated with the intake of these vasoconstrictors, including 83 neuropsychiatric effects, 4 cardiovascular problems and 2

		deaths. Therefore the French Agency of Medicines has restricted the use of pseudoephedrine and phenylpropanolamine products for adults. (Reference: Letter from the Directorate of Medicines and Pharmacy, Rabat, 24 August 1999.)
Oman	2000	The Directorate General of Pharmaceutical Affairs & Drug Control has restricted the prescribing of any preparation containing phenylproanolamine hydrochloride or pseudoephedrine hydrochloride to adults and children over 2 years of age. This action has been taken following the results of research performed by the French Commission for Pharmacovigilance which revealed serious risks to health associated with the intake of these vasoconstrictors in paediatric use. (Reference Circular No. 3/2000 Directorate General of Pharmaceutical Affairs, Ministry of Health, Sultanate of Oman, 13 May 2000.)

Product name: **Streptomycin and penicillin**

Country	Effective Date	Description of action taken Grounds for decision
India	January 1998	The Ministry of Health and Family Welfare, Department of Health, has prohibited the manufacture and sale of parenteral preparations containing fixed dose combinations of streptomycin with penicillins because it has been concluded that fixed dose combinations of streptomycin with penicillins do not have the therapeutic value claimed or purported to be claimed for them. (Reference: The Eastern Pharmacist, September 1997.)

Product name: **Trancylopramine and trifluoperazine**

Country	Effective Date	Description of action taken Grounds for decision
United Kingdom	1999	The licence for the antidepressant, trancylopramine and trifluorperazine has not been renewed by the Committee on Safety of Medicines because of concerns over drug interactions and the risk of severe hypertensive crises. As a result the company have withdrawn the product from the market. (Reference: Current Problems in Pharmacovigilance Vol. 25, June 1999.)

Product name: **Anorectic agents**

Country	Effective Date	Description of action taken Grounds for decision
France	October 1999	The Agency Française de Sécurité Sanitaire des Produits de Santé (AFSSPS) has suspended the marketing authorizations for medicinal products containing the anorectic agents amfepramone, clobenzorex, dexfenfluramine, fenfluramine, fenproporex and mefenorex because of their implication in the occurrence of arterial pulmonary hypertension. (Reference: La Revue Prescrire Vol. 19, No.199, October 1999.)
Oman	April 2000	The Directorate General of Pharmaceutical Affairs & Drug Control has banned the registration and import of the following anorectic agents: Clobenzorex, mefenorex, phedimetrazine, fenproporex, nor pseudoehedrine, febutazate and propylhexedrine. This action was taken because of lack of therapeutic efficacy leading to an unfavourable benefit/risk balance. . (Reference Circular No. 26/2000 Directorate General of Pharmaceutical Affairs, Ministry of Health, Sultanate of Oman, 26 April 2000.)
Portugal	September 1999	The Portuguese Medicines Evaluation Committee has recommended to the Board of INFARMED the suspension of marketing authorizations for all medicinal products containing clobenzorex and fenproporex. This recommendation follows the final opinions of the Committee on Proprietary Medicinal Products that recommends the withdrawal of the marketing authorizatons for medicinal products containing amfepramone, phentermine, clobenzorex, fenproporex, mefenorex, norpseudoephedrine and phendimetrazine based on the lack of therapeutic efficacy of these products leading to an unfavourable benefit/risk balance and the withdrawal of the marketing authorizations for fenfluramine and dexfenfluramine containing medicinal products, based on an unacceptable safety profile under normal conditions of use and limited therapeutic efficacy, leading to an unfavourable benefit/risk balance. (Reference: Communication from the Instituto Nacional da Farmacia e do Medicamento (INFARMED), Lisbon, 14 September 1999.)

Product name: **Ionic contrast media**

Country	Effective Date	Description of action taken Grounds for decision
Germany	July 1998	The Federal Institute of Drugs and Medical Devices has announced its intention to revoke the marketing authorizations for ionic contrast media containing lysine amidotriazoate, iotalamic acid or ioxitalamic acid, either alone or in combination, for intravasal administration, because their use has been associated with severe adverse reactions including

		hypotension, arrhythmias, pulmonary oedema and renal disorders. (Reference: Notification from the Federal Institute for Drugs and Medical Devices, 6 July 1998.)

Product name: **Mercuric derivatives (topical)**

Country	Effective Date	Description of action taken Grounds for decision
Canada	April 1997	Health Canada has warned consumers not to use DianaR Cream (Diana de Beauté), a product that is used for skin lightening, mainly by Afro and Caribbean communities. The product, which is manufactured in the Lebanon, has not been approved for sale in Canada and is being illegally imported. It contains ammoniated mercury, bismuth subnitrate and salicylic acid and the mercury content poses a high risk of mercury poisoning in adults and a serious health hazard to unborn and nursing infants of women who use the product. (Reference: Press Release, Health Canada, 1997-28, 18 April 1997.)

Product name: **Pyrethroids**

Country	Effective Date	Description of action taken Grounds for decision
Oman	1997	The Directorate General of Pharmaceutical Affairs & Drug Control has prohibited the registration, import and sale of pyrethroids such as bioallethrin, permethrin, phenothrin, tetramethrin and carbaril in all parasiticidal preparations because of a potential risk of carcinogenicity. (Reference: Pharmaceutical Newsletter 5(4): 8 (1997), Ministry of Health, Muscat.)