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"Consolidated List of Products whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments"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 Eighth Issue - August 2005

Medicines Policy and Standards
Quality Assurance and Safety: Medicines
Health Technology and Pharmaceuticals

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This text is the update to the Eighth Issue of the United Nations Consolidated List of Products whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments - Pharmaceuticals (UN General Assembly Resolutions 37/137, 1982; 38/149, 1983; 39/229, 1984; 44/226, 1989).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 early April 2005.

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 20 governments on 44 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 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

Combination Products

Group 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
Spain	June 2003	The Spanish Medicines Agency has withdrawn all paediatric over-the-counter (OTC) medicinal preparations containing salicylates/acetylsalicylic acid (Aspirin) from the market. This measure has been undertaken to prevent the use of these products in children with viral fever due to the risk of Reye's syndrome. The Summary of Product Characteristics (SPC) for non-paediatric OTC products containing salicylates/acetylsalicylic acid has been modified to note that: • Salicylates/acetylsalicylic acid–containing OTC products for adult use are contraindicated in children below the age of 16 years. • Salicylates/acetylsalicylic acid–containing prescription products are contraindicated for the treatment of fever, chickenpox and viral fevers in patients below 16 years of age. **References:** 1. Communication from the Spanish Pharmacovigilance System, 8 July 2003. 2. WHO Pharmaceuticals Newsletter No. 4, 2003.
UK	October 2003	According to the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) the labels of all acetylsalicylic acid-containing products are required to include the following statutory label warning: "Do not give to children under 16 years, unless on the advice of a doctor". This requirement follows an eight-week consultation process after which the Medicines Commission endorsed the advice of the UK Committee on Safety of Medicines that the warning was required. **Reference:** Medicines and Healthcare products Regulatory Agency. Internet Document, 4 April 2003 (http://www.mhra.gov.uk).

Product Name: **Adalimumab**

CAS number: 331731-18-1

Scientific and Common Names, Synonyms: Humira

Country	Effective Date	Description of action taken Grounds for decision
USA	November 2004	Label to contraindicate concurrent use of adalimumab and anakinra a Tumor Necrosis Factor (TNF)-blocking agent since serious infections were seen in clinical studies with the concurrent use of anakinra and another TNF blocking agent. **References:** 1. 'Dear Health-care Professional' letter from Abbott Laboratories, 5 November 2004 (http://www.fda.gov). 2. WHO Pharmaceuticals Newsletter No. 6, 2004.

Product Name: **Amphetamine**

CAS number: 68844-77-9

Scientific and Common Names, Synonyms: Adderall, Adderall XR

Country	Effective Date	Description of action taken Grounds for decision
Canada	9 February 2005	Health Canada has suspended the marketing of amphetamine preparations (Adderall, Adderall XR) used in Attention Deficit Hyperactivity Disorder (ADHD) due to 20 international reports of sudden deaths in paediatric and adult patients in association with amphetamine (Adderall, Adderall XR) use. **References:** 1. Health Canada Warnings/Advisories, 9 February 2005 (http://www.hc-sc.gc.ca). 2. WHO Pharmaceuticals Newsletter No. 2, 2005.

Product Name: Anagrelide

CAS number: 68475-42-3

Scientific and Common Names, Synonyms: 6,7-Dichloro-1,5-dihydroimidazo[2,1-b]quinazolin-2(3H)one;

Agrylin

Country	Effective Date	Description of action taken Grounds for decision
USA	January 2005	Prescribers are advised against using the product in patients with severe hepatic impairment, and to reduce the dose in patients with moderate hepatic impairment. The advice is based on pharmacokinetic studies that revealed an eight-fold increase in total exposure to anagrelide in patients with moderate hepatic impairment. **References:** 1. 'Dear Health-care Professional' letter from Shire Development Inc., January 2005 (http://www.fda.gov). 2. WHO Pharmaceuticals Newsletter No. 2, 2005.

Product Name: Aristolochic Acid

CAS number: 68475-42-3

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
The People's Republic of China	30 September 2004	China's State Food and Drug Administration (SFDA) has banned two commonly used herbs containing aristolochic acid, a toxin reported to be linked to kidney failure and cancer. Manufacturers have been directed to replace *Aristolochia fangchi* and *Aristolochia debilis* with *Stephania tetrandra* and *Inula helenium* respectively, in their traditional medicine formulations. **Reference:** WHO Pharmaceuticals Newsletter No. 5, 2004.

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
Argentina	19 August 2003	The Food, Drug and Medical Devices agency in Argentina, ANMAT has withdrawn all medicinal products containing astemizole since these products have the potential to cause life-threatening ventricular arrhythmias. **Reference:** Communication from ANMAT, 19 August 2003 (http://www.anmat.gov.ar)
Spain	8 April 2003	The Spanish Medicines Agency has withdrawn the marketing authorization for 10 medicinal products containing astemizole due to the potential of these products to produce life-threatening ventricular arrhythmias. **Reference:** Communication from the Spanish Medicines Agency, 8 April 2003 (http://www.msc.es/agemed/csmh/notas/astemizol.asp).

Product Name: Benfluorex

CAS number: 23602-78-0

Scientific and Common Names, Synonyms: Benfluorexum

Country	Effective Date	Description of action taken Grounds for decision
Spain	April 2003	The marketing authorization of the only medicinal product with benfluorex (Modulator capsules) was revoked at the request of the marketing authorization holder, Servier. A case of cardiac valvulopathy associated with the use of benfluorex (Modulator capsules) has been published in Spain.

		Reference: Communication from the Pharmacoepidemiology and Pharmacovigilance Division of the Spanish Medicines and Health products Agency (SMHA), Madrid, Spain, April 2003.

Product Name: Benzbromarone

CAS number: 3562-84-3

Scientific and Common Names, Synonyms: Desuric

Country	Effective Date	Description of action taken Grounds for decision
France	April 2003	The hyperuricaemic product benzbromarone (Desuric) has been withdrawn in France following reports of serious liver damage associated with its use. **References:** 1. WHO Pharmaceuticals Newsletter No. 4, 2003. 2. Chaibriant H. Stop marketing of proprietary medical product DESURIC(Rm)(benzbromarone), 22 April 2003 (http://www.agemed.sante.gouv.fr).
Portugal	April 2003	Suspended due to unfavourable benefit-risk evaluation. **Reference:** Communication from INFARMED, Portuguese Regulatory Agency, April 2003.

Product Name: Bicalutamide

CAS number: 90357-06-5

Scientific and Common Names, Synonyms: ICI-176334;

Casodex

Country	Effective Date	Description of action taken Grounds for decision
Canada	18 August 2003	Withdrawn due to reports of accelerated deaths of patients with localized prostate cancer.

		Reference: Health Canada Warnings and Advisories, 18 August 2003.
UK	28 October 2003	Withdrawn due to clinical trial data showing an increased number of deaths in patients with localized prostate cancer. **Reference:** Communication from the Committee on Safety of Medicines, 28 October 2003 (http://www.mhra.gov.uk).

Product Name: *Camelia sinensis*

CAS number:

Scientific and Common Names, Synonyms: Exolise

Country	Effective Date	Description of action taken Grounds for decision
France, Spain	April 2003	The French and Spanish Advisory Boards have suspended the marketing authorization of a Green Tea (*Camelia sinensis*) product (Exolise), prepared from the ethanolic extract of Green Tea, due to several reports of hepatic disorders. **References:** 1. Communication from the Spanish Pharmacovigilance System, 11 April 2003. 2. Spanish Medicines Agency Press Release, 7 April 2003 (http://www.msc.es/agemed/csmh/notas/exolise.asp).

Product Name: Celecoxib

CAS number: 169590-42-5

Scientific and Common Names, Synonyms: Celebrex

Country	Effective Date	Description of action taken Grounds for decision
The Republic of Turkey	November 2004	The Market Authorization Holder for celecoxib (Celebrex) in the Republic of Turkey has voluntarily withdrawn celebrex from the Turkish market. **Reference:** Press Release from the Turkish Ministry of Health and Communication from the Turkish Clinical Pharmacological Society, November 2004.

Product Name: Cisapride

CAS number: 81098-60-4

Scientific and Common Names, Synonyms: *cis*-4-Amino-5-chloro-N-(1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidyl)-2-methoxybenzamide monohydrate;

Cisapridum

Country	Effective Date	Description of action taken Grounds for decision
Australia	2002	The highest strength cisapride tablets have been withdrawn and the product information has been revised for all the other cisapride preparations. All patients now require measurements of renal function and ECGs before and during treatment. Concerns about cardiac arrhythmias led to these measures. **References:** 1. Australian Prescriber 25, No. 6, 2002 (http://www.australianprescriber.com). 2. WHO Pharmaceuticals Newsletter No. 1, 2003.

Product Name: Codeine

CAS number: 76-57-3

Scientific and Common Names, Synonyms: 7,8-Didehydro-4,5-epoxy-3-methoxy-17-methyl-morphinan-6-ol monohydrate;

Codol, Codicept

Country	Effective Date	Description of action taken Grounds for decision
Malaysia	31 December 2002	The Drug Control Authority in Malaysia has cancelled the registration of all liquid codeine-containing preparations due to the growing problem of codeine misuse and abuse in Malaysia. **Reference:** Berita Ubat-ubatan, August 2002, 19:5.

Product Name: Danazol

CAS number: 17230-88-5

Scientific and Common Names, Synonyms: 17α-Pregna-2,4-dien-20-yno[2,3-d]isoxazol-17β-ol;

Danol

Country	Effective Date	Description of action taken Grounds for decision
UK	September 2003	The use of danazol has been restricted to second-line therapy in endometriosis and benign fibrocystic breast disease due to the potential for an increase in the baseline risk of ovarian cancer in patients treated for endometriosis. **Reference:** WHO Pharmaceuticals Newsletter No. 5, 2003.

Product Name: Desloratadine

CAS number: 100643-71-8

Scientific and Common Names, Synonyms: Descarboethoxyloratadine;

Aerius, Opulis

Country	Effective Date	Description of action taken Grounds for decision
Europe	January 2003	As a precautionary measure, use not recommended during pregnancy although a causal relationship between hypospadias (a urogenital abnormality) and the use of products containing loratadine during pregnancy have not been confirmed or excluded. **Reference:** European Agency for the Evaluation of Medicinal Products' (Committee for Proprietary Medicinal Products) December 2002 plenary meeting monthly report, 6 January 2003 (http://www.emea.eu.int).

Product Name: **Ephedra**

CAS number:

Scientific and Common Names, Synonyms: Efedra, Ma-huang

Country	Effective Date	Description of action taken Grounds for decision
Jordan	January 2004	The Jordan Food and Drug Administration has withdrawn a herbal product (Magic Herb), used to promote weight loss, on the grounds that it contains ephedra. This decision was based on the US FDA's website information about the unreasonable risk in using food supplements containing ephedra or ephedrine. **Reference:** Communication from Jordan Pharmacovigilance Centre, 19 January 2004.
The Netherlands	12 April 2004	According to the Ministry of Health in the Netherlands, ephedra herbal products may only be sold as medicinal products there. **Reference:** News and Publications from Medicines Evaluation Board, the Netherlands, 18 February 2004 (http://www.cbg-meb.nl/uk/nieuws).
USA		The FDA has prohibited the sale of dietary supplements containing ephedrine alkaloids (ephedra) on the grounds that such supplements present an unreasonable risk of illness or injury. **Reference:** FDA Statement, 12 April 2004 (http://www.fda.gov).

Product Name: **Epoetin alfa**

CAS number: 113427-20-0

Scientific and Common Names, Synonyms: Eprex

Norway	June 2002	The Norwegian Medical Agency alerted physicians to the occurrence of epoetin alfa-related pure red cell aplasia (PRCA) and to a corresponding label change recommending the intravenous route for epoetin alfa in patients with chronic renal failure. At the time of this action one case of PRCA related to subcutaneous use of epoetin alfa had been reported. **Reference:** Harg P, Buajordet I, Madsen S. Eprex should be administered

		intravenously in order to reduce the risk for erythroplasia. Nytt om Legemidler, 8 November 2002, 25:8.
UK	June 2002	Warning issued against subcutaneous administration in patients with chronic renal failure since it could precipitate pure red cell aplasia (PRCA) in these patients. **Reference:** Communication from Chairman, Committee on Safety of Medicines, UK, (Ref. CEM/CMO/2002/17), 12 December 2002 (http://www.info.doh.gov.uk).

Product Name: Levacetylmethadol

CAS number: 34433-66-4

Scientific and Common Names, Synonyms: (-)-6-(Dimethylamino)-4,4-diphenyl-3-heptanol acetate; Orlaam, Levomethadylacetate

Country	Effective Date	Description of action taken Grounds for decision
USA	2003	Withdrawn due to adverse cardiac events; safer alternatives to be adopted. **Reference:** 'Dear Health-care Professional' letter from Roxane Laboratories Inc., 23 August 2003 (http://www.fda.gov).

Product Name: Loratadine

CAS number: 79794-75-5

Scientific and Common Names, Synonyms: Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]piperidine-1-carboxylate

Country	Effective Date	Description of action taken Grounds for decision
Europe	November 2003	The European Committee for Proprietary Medicinal Products (CPMP) has advised against the use of loratadine during pregnancy. This advice was issued as a precautionary measure following a EU-wide review that could neither confirm nor exclude a causal relationship between loratadine and hypospadias in new-born boys born to mothers receiving loratadine.

		Reference: EMEA Press Release EMEA/CPMP/5732/03/Final, 20 November 2003 (http://www.emea.eu.int).

Product Name: Muromonab-CD3

CAS number:

Scientific and Common Names, Synonyms: Orthoclone OKT3

Country	Effective Date	Description of action taken Grounds for decision
Canada	2004	Not approved for paediatric use (age up to 17 years) due to risk of serious adverse reactions such as cerebral oedema and herniation in paediatric patients treated with this product. **Reference:** Letter to Hospital Chief Medical Staff, from Janssen-Ostho Inc., 13 May 2004 (http://www.hc-sc.gc.ca).

Product Name: Natalizumab

CAS number: 189261-10-7

Scientific and Common Names, Synonyms: Tysabri

Country	Effective Date	Description of action taken Grounds for decision
USA	2005	Biogen Idec voluntarily suspended marketing of natalizumab due to serious adverse event reports of progressive multifocal leukoencephalopathy in clinical trials. **Reference:** US FDA Public Health Advisory, 28 February 2005 (http://www.fda.gov).

Product Name: Nefazodone hydrochloride

CAS number: 82752-99-6

Scientific and Common Names, Synonyms: 2-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl}-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-1,2,4-triazol-3-one monohydrochloride;

Serzone

Country	Effective Date	Description of action taken Grounds for decision
Canada	27 November 2003	The sale of nefazodone has been discontinued in Canada due to adverse hepatic events. **Reference:** 'Dear Health-care Professional' letter from Bristol-Myers Squibb Canada, 2 October 2003 (http://www.hc-sc.gc.ca).
Singapore	1 March 2003	Withdrawn by the company due to low usage of the drug in Singapore. **Reference:** Product Safety Alert, Health Sciences Authority, Singapore, 29 July 2004 (http://www.hsa.gov.sg).
Spain	1 March 2004	Nefazodone has been suspended due to life-threatening hepatotoxicity. **Reference:** Spanish Medicines Agency (http://www.msc.agemed/csmh/notas/nefazodona.asp).
The Republic of Turkey	2003	The Directorate General of Pharmaceuticals and Pharmacy has suspended the license for nefazodone hydrochloride preparations (Serzone) held by Bristol Myers Squibb Drugs Inc., in the Republic of Turkey since latest data received by the Turkish Ministry of Health as well as worldwide developments suggest acute hepatic failure associated with nefazodone use. **Reference:** Communication from *the Division of Pharmacovigilance,* Ministry of Health, the Republic of Turkey, 21 March 2003.

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',3'-e][1,4]diazepin-6-one;

Viramune, Nevimune

Country	Effective Date	Description of action taken Grounds for decision
USA	2005	Not recommended in women with CD4+ cell counts greater than 250 cells/mm3 based on the observation that these women have a much higher risk of symptomatic liver toxicity associated with nevirapine use than females with CD4+ cell counts <250 cells/mm3. **References:** 1. WHO Pharmaceuticals Newsletter No. 1, 2005. 2. FDA Public Health Advisory for Nevirapine, 20 January 2005 (http://www.fda.gov).

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
Argentina	2003	The food, drug and medical devices agency in Argentina, ANMAT, has directed that nimesulide should be brought under the category of products under 'special pharmacovigilance'. This category includes those drugs that are put under high alert and scrutiny for adverse reactions. Manufacturers are obliged to report all adverse effects associated with nimesulide use. **Reference:** *Disposicion* de ANMAT no 4087/03, August 2003.

Bangladesh	2003	The manufacture, distribution, sale and use of all dosage forms of nimesulide paediatric preparations have been banned. **Reference:** Communication to WHO, Geneva, from Director, Directorate of Drug Administration, Ministry of Health and Family Welfare, Bangladesh, 11 June 2003.

Product Name: Oseltamivir

CAS number: 196618-13-0

Scientific and Common Names, Synonyms: Ethyl(3R,4R,5S)-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate phosphate(1:1);

Tamiflu

Country	Effective Date	Description of action taken Grounds for decision
USA	2004	Not indicated for either treatment or prophylaxis of influenza in children under one year of age due to the uncertainty in predicting the oseltamivir exposure outcomes in infants with immature blood-brain barriers. **Reference:** 'Dear Health-care Professional' letter from Roche Laboratories Inc., December 2003 (http://www.fda.gov).

Product Name: Paroxetine

CAS number: 61869-08-7

Scientific and Common Names, Synonyms: (-)-trans-5-(4-p-Fluorophenyl-3-piperidyl-methoxy)-1,3-benzodioxole;

Seroxat

Country	Effective Date	Description of action taken Grounds for decision
Canada	2003	Not to be used in children and adolescents under the age of 18 years to treat depressive illness due to unfavourable risk-benefit ratio.

		References: 1. 'Dear Health-care Professional' letter from GlaxoSmithKline Inc., 10 July 2003 (http://www.hc-sc.gc.ca). 2. WHO Pharmaceuticals Newsletter No. 4, 2003.
UK	2003	Not to be used in children and adolescents under the age of 18 years to treat depressive illness due to unfavourable risk-benefit ratio. **References:** 1. Letter from the Chairman of the Committee on Safety of Medicines, 10 June 2003 (http://www.medicines.mhra.gov.uk). 2. WHO Pharmaceuticals Newsletter No. 4, 2003.

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
Japan	2003	The Ministry of Health, Labour and Welfare (MHLW) has asked manufacturers of products containing phenylpropanolamine (PPA) to include new warnings on cardiovascular risks in the product label. The move follows several reports of cerebral haemorrhage and other problems associated with the use of PPA containing products. **Reference:** WHO Pharmaceuticals Newsletter No. 5, 2003.
The Republic of Korea	1 August 2004	The Korean Food and Drug Administration (KFDA) has banned the production and sale of about 170 prescription and over-the-counter cold remedies containing phenylpropanolamine (PPA). The ban follows the conclusions of a Korean study that PPA-containing drugs may be associated with strokes. **References:** 1. Korean News Media, August 2004. 2. WHO Pharmaceuticals Newsletter No. 5, 2004.

Product Name: **Promethazine**

CAS number: 58-33-3

Scientific and Common Names, Synonyms: Dimethyl (1-methyl-2-phenothiazin-10-ylethyl)amine;

Phenergan

Country	Effective Date	Description of action taken Grounds for decision
The Sultanate of Oman	March 2005	Physicians are warned that promethazine formulations are contraindicated in children under two years of age; and to exercise caution while administering these products in older paediatric patients. This advice follows the US post-marketing report of respiratory depression, including fatality associated with promethazine-use in children under two years of age. **Reference:** Circular No. 14/2005, Directorate General of Pharmaceutical Affairs and Drug Control, Ministry of Health, the Sultanate of Oman, 2 March 2005.
USA	January 2005	The Contraindications, Warnings/Use in Paediatric Patients and Dosage and Administration sections of the labels have been revised to warn against using these products in children below the age of two due to the risk of fatal respiratory depression. This warning is based on post-marketing reports of respiratory depression including fatalities associated with the use of promethazine hydrochloride preparations in paediatric patients of this age group. Caution is needed when using this product in children two years of age and older. **Reference:** 'Dear Health-care Professional' letter from Wyeth Pharmaceuticals, 21 January 2005 (http://www.fda.gov).

Product Name: Repaglinide

CAS number: 135062-02-1

Scientific and Common Names, Synonyms: (+)-2-Ethoxy-α-{[(S)-α-isobutyl-o-piperidinobenzyl]carbamoyl}-p-toluic acid;

Prandin, Novonorm

Country	Effective Date	Description of action taken Grounds for decision
Canada	2002	The concomitant use of repaglinide and gemfibrozil has been contraindicated, following the publication of a study in healthy volunteers demonstrating a markedly enhanced blood glucose-lowering response to repaglinide (GlucoNorm) when given along with gemfibrozil. The Canadian drug safety database contains five reports of serious hypoglycaemia in patients receiving concomitant repaglinide and gemfibrozil. **Reference:** 'Dear Health-care Professional' letter from Novo Nordisk Canada Inc., 17 July 2002 (http://www.hc-sc.gc.ca).
Europe	2003	Not to be used along with gemfibrozil since the blood glucose lowering effect of repaglinide maybe markedly enhanced and prolonged when administered together with gemfibrozil, with an increased risk of severe hypoglycaemia. **Reference:** EMEA Public Statement (EMEA/11700/03), 21 May 2003 (http://www.emea.eu.int).

Product Name: Rofecoxib

CAS number: 162011-90-7

Scientific and Common Names, Synonyms: 4-[p-(Methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone;

Vioxx, Coxxil

Country	Effective Date	Description of action taken Grounds for decision

Italy	30 September 2004	All pharmaceutical preparations containing rofecoxib, namely Arofexx, Coxxil, Dolcoxx, Dolostop and Miraxx have been withdrawn from the Italian market. **Reference:** Communication received in WHO, Geneva, October 2004.
Portugal	October 2004	All six brands of rofecoxib authorized in Portugal (Vioxx, Coxxil, Acoxxin, Ceoxx, Dolocoxx and Trioxx) were withdrawn from the market. **Reference:** Communication from Directora do Departamento de Farmacovigilancia, October 2004.
Spain	1 October 2004	The Spanish Medicines Agency has authorized the withdrawal of all medicinal products with rofecoxib: Vioxx, Ceoxx, Recox. **Reference:** Comunicación sobre riesgos de medicamentos para profesionales sanitarios, Ref: 2004/ 10, 30 September 2004 (http://www.agemed.es/documentos/notasPrensa/csmh/2004/cont_rofecoxib.htm).
Turkey	1 October 2004	Various proprietary preparations of rofecoxib (brand names: Vioxx, Ecrox, Romaryd, Reox, Raxtane, Rofenax, Vioref) have been withdrawn from the market. **Reference:** Pharmacovigilance Unit, TADMER, Ankara, Turkey.
Worldwide	30 September 2004	Merck & Co voluntarily withdrew rofecoxib (Vioxx) from the world market due to safety concerns of an increased risk of cardiovascular events (including heart attack and stroke) in patients treated with rofecoxib. **Reference:** Merck & Co Press Release, 30 September 2004 (http://www.merck.com).

Product Name: **Salmeterol**

CAS number: 89365-50-4

Scientific and Common Names, Synonyms: Serevent

Country	**Effective Date**	**Description of action taken** **Grounds for decision**

Canada	August 2003	Salmeterol (Serevent) is not approved as monotherapy for asthma, should not be used alone for the maintenance treatment of asthma and is not a substitute for inhaled or oral corticosteroids. Salmeterol (Serevent) is a long-acting beta-2-agonist and a 'controller' medication for preventing asthma symptoms like wheezing, shortness of breath and coughing. It is to be used as an add-on therapy in those patients already managed with appropriate maintenance doses of inhaled corticosteroids. These decisions have been based on the Salmeterol Multi-center Asthma Research Trial (SMART) that was halted in the US due to an increase in asthma-related deaths in patients receiving salmeterol (Serevent) compared with those receiving placebo. **References:** 1. 'Dear Health-care Professional' letter from GlaxoSmithKline Inc., 15 August 2003 (http://www.hc-sc.gc.ca). 2. Public Advisory from GlaxoSmithKline Inc., 4 September 2003 (http://www.hc-sc.gc.ca).
USA	August 2003	The US FDA has advised that all drug products containing salmeterol should include new safety information and warnings about a small but significant number of reports of life-threatening asthma episodes or asthma-related deaths in patients taking these products. The FDA announcement is based on observations from the SMART study. **Reference:** FDA Talk Paper, 14 August 2003 (http://www.fda.gov).

Product Name: **Valdecoxib**

CAS number: 181695-72-7

Scientific and Common Names, Synonyms: p-(5-Methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide;

Bextra

Country	Effective Date	Description of action taken Grounds for decision
USA	2005	The US FDA has asked Pfizer to withdraw valdecoxib (Bextra) from the market because of: • lack of adequate data on the cardiovascular safety of long-term use of valdecoxib (Bextra), along with the increased risk of adverse cardiovascular events in short-term coronary artery bypass surgery (CABG) trials; • reports of serious and potentially life-threatening skin reactions, including deaths, in patients using valdecoxib and, • lack of any demonstrated advantages for valdecoxib compared with other non-steroidal anti-inflammatory drugs (NSAIDs).

Reference:
Public Health Advisory, 7 April 2005 (http://www.fda.gov).

Product Name: Venlafaxine hydrochloride

CAS number: 99300-78-4

Scientific and Common Names, Synonyms: (RS)-1-(2-Dimethylamino-1-p-methoxyphenylethyl)cyclohexanol hydrochloride;

Effexor

Country	Effective Date	Description of action taken Grounds for decision
Canada and USA	September 2003	A letter was issued to doctors with the information that, efficacy was not established for major depressive disorder (MDD) or generalized anxiety disorder (GAD) with venlafaxine in clinical studies in paediatric patients (ages 6 to 17), and that there were increased reports among those patients on venlafaxine vs. placebo, of hostility and suicide-related adverse events, such as suicidal ideation and self-harm. Additionally, health professionals were also reminded that in Canada, venlafaxine is not recommended for use in patients under 18 years of age. **References:** 1. 'Dear Health-care Professional' letter from Wyeth Pharmaceuticals, 10 September 2003 (http://www.hc-sc.gc.ca). 2. 'Dear Health-care Professional' letter from Wyeth Pharmaceuticals, 22 August 2003 (http://www.fda.gov).
Sweden	September 2003	The Medical Products Agency (MPA) has advised all those health professionals who prescribe venlafaxine in children to be alert to suicidal thoughts in these patients and pointed out that venlafaxine is not approved for use in this age group. **Reference:** WHO Pharmaceuticals Newsletter No. 5, 2003.
UK	September 2003	The Expert Working Group of the Committee on Safety of Medicines (CSM) has advised that venlafaxine should not be used in children under the age of 18 years for the treatment of depressive illness since results from clinical trials do not demonstrate the safety and efficacy of venlafaxine in depressive illness in this population. **Reference:** Message from Professor G. Duff, Chairman, Committee on Safety of Medicines, 19 September 2003 (http://www.medicines.mhra.gov.uk).

Product Name: Abacavir, Lamivudine, Tenofovir

Country	Effective Date	Description of action taken Grounds for decision
Europe	July 2003	Physicians are warned that abacavir and lamivudine in combination with tenofovir should not be used as a triple antiretroviral therapy when considering a new treatment regimen for naÏve or pre-treated patients and particularly, as once-daily regimen. This warning is based on reports of a high rate of early virologic non-response observed in a clinical study of therapy naÏve patients receiving combination therapy of the three drugs. **Reference:** EMEA Public Statement, 30 July 2003, EMEA/20194-03 (http://www.emea.eu.int).

Product Name: Atazanavir-Ritonavir

Country	Effective Date	Description of action taken Grounds for decision
Europe	December 2004	The European Medicines Agency (EMEA) has issued a public statement warning against the co-administration of atazanavir (Reyataz) combined with ritonavir (RTV) and 40 mg omeprazole, a proton pump inhibitor, to avoid risk of reduction in the atazanavir exposure levels in these patients. This warning is based on the observations from a randomized, open-label, multiple-dose drug interaction study performed in healthy volunteers that demonstrated a 76% reduction in atazanavir area under the concentration curve (AUC) and a 78 % reduction in atazanavir trough plasma concentration (Cmin) when atazanavir-ritonavir (300/100 mg) was co-administered with omeprazole (40 mg) proton pump inhibitor. **Reference:** EMEA Public Statement, EMEA/CHMP/202649/2004, 21 December 2004 (http://www.emea.eu.int).

Product Name: Benziodarone and Benzbromarone-Allopurinol

Country	Effective Date	Description of action taken Grounds for decision

Spain	February 2004	Following reports of hepatotoxicity, the Spanish Safety Committee has withdrawn the marketing authorizations for benziodarone and benzbromarone-allopurinol fixed dose combination products. Benzbromarone has been brought under restricted use, to be prescribed by specialists (rheumatologists or nephrologists) in hospitals, for treating hyperuricaemia in allopurinol-intolerant patients with: • gout polyarticular or gout tophaceous • renal failure • renal transplantation. **Reference:** Press Release from the Spanish Agency for Medicines and Medical Devices (Agencia Espanola de Medicamentos y Productos Sanitarios), Ref: 2004/02, 10 February 2004 (http://www.msc.es/agemed).

Product Name: Didanosine, Lamivudine, Tenofovir

Country	Effective Date	Description of action taken Grounds for decision
Europe	October 2003	Physicians are warned that tenofovir, in combination with didanosine and lamivudine should not be used as a triple antiretroviral therapy when considering a new treatment regimen for naive or pre-treated patients with HIV-infections and particularly, as a once-daily regimen. This advice is based on the high rate of early virologic failure and emergence of nucleoside/nucleotide reverse transcriptase inhibitor resistance associated mutations observed in HIV-patients treated with a once-daily combination of the three drugs. **References:** 1. EMEA Public Statement, 22 October 2003, EMEA/CPMP/5094/03 (http://www.emea.eu.int). 2. WHO Drug Alert 109, 24 October 2003 (http://www.who.int/medicines/library/drugalert).

Product Name: Paracetamol-Dextropropoxyphene

Country	Effective Date	Description of action taken Grounds for decision

UK	January 2005	The UK Medicines and Healthcare products Regulatory Agency (MHRA), under advice from its Committee on Safety of Medicines (CSM), has announced the withdrawal of the paracetamol-dextropropoxyphene combination product (co-proxamol) in the UK. The CSM undertook a review of the risks and benefits of co-proxamol and concluded that the efficacy of co-proxamol is poorly established and that the risk of toxicity in overdose, both accidental and deliberate, is unacceptable. **Reference:** Letter from the Chairman, UK Committee on Safety of Medicines, 31 January 2005 (http://www.mhra.gov.uk).

Product Name: Rifampicin and Pyrazinamide

Country	Effective Date	Description of action taken Grounds for decision
France	2004	Revised recommendations on the use of combination rifampicin and pyrazinamide for latent tuberculosis in patients receiving infliximab (Remicade) have been issued by the French regulatory authority, l'Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), following reports of serious and sometimes fatal hepatitis. AFSSAPS advises that the combination of rifampicin and pyrazinamide should be avoided and that the combination of rifampicin and isoniazid be used instead or, alternatively, isoniazid alone in elderly patients, in patients with cirrhosis or in the event of toxicity. **Reference:** French Health Products Safety Agency, 20 August 2004 (http://www.afssaps.sante.fr).
USA	2003	The US Federal health officials are warning physicians against prescribing rifampicin-pyrazinamide combination for the treatment of latent tuberculosis (TB) due to high rates of hospitalization and death from liver injury associated with the combined use of these drugs. However the combination could be considered in patients with active TB or in patients unlikely to complete a nine-month course of isoniazid. **Reference:** Letter from The Centers for Disease Control and Prevention (CDC), 8 August 2003 (http://www.cdc.gov).

Product Name: Cyclooxygenase-2 Inhibitors

Country	Effective Date	Description of action taken Grounds for decision
Australia	2005	The Therapeutic Goods Administration (TGA) has directed manufacturers of cyclooxygensae-2 (COX-2) inhibitor drugs to place new highlighted explicit warnings in product information about the increased risk of cardiovascular adverse events from this group of drugs. The new warning statements are to be highlighted with a black boxed margin. In addition, TGA will cancel the registration of the drug parecoxib (Dynastat) because of the risk of cardiovascular events and, greatly limit the approved uses of two other COX-2 inhibitors, etoricoxib and lumiracoxib. These recommendations were based on the advice of the Australian Drug Evaluation Committee. **Reference:** TGA Media Statement, 10 February 2005 (http://www.tga.gov.au).
Europe	2005	The following urgent safety restrictions have been taken for COX-2 inhibitors available in the European Union: • A contraindication is introduced for all COX-2 inhibitors in patients with ischaemic heart disease or stroke. • As a further measure, a contraindication is introduced for etoricoxib in patients with hypertension (high blood pressure) whose blood pressure is not under control. • A warning is introduced for prescribers to exercise caution when prescribing COX-2 inhibitors for patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking, as well as for patients with peripheral arterial disease. • Given the association between cardiovascular risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment. **Reference:** EMEA Public Statement, EMEA/62838/2005, 17 February 2005 (http://www.emea.eu.int).
New Zealand	2005	COX-2 inhibitors are not recommended: • for routine use in patients with rheumatoid arthritis or osteoarthritis except where the patient is at "high risk" of developing a serious gastrointestinal adverse effect from other standard non-steroidal anti-inflammatory agents; • for patients at high risk of heart attack or stroke; • for patients already taking aspirin; • for routine relief of post-operative pain.

Patients already taking COX-2 inhibitors on a regular basis should discuss the continuing use of these medicines with their general practitioner or specialist. Prescribers should discuss with their patients the available alternatives, and review the risks and benefits of these alternatives compared with the emerging clinical concerns about COX-2 inhibitors, before deciding on the best course of treatment for that individual.

Reference:
MEDSAFE (New Zealand Medicines and Medical Devices Safety Authority) Alert/Letter, 22 February 2005 (http://www.medsafe.govt.nz).

Product Name: Dietary Supplements

Country	Effective Date	Description of action taken Grounds for decision
USA	2003	Two dietary supplement products (Vinarol from Ultra Health Laboratories Inc., and Bionate Inc., and Viga from Best Life International) have been voluntarily recalled by the respective companies due to the unlabeled presence of sildenafil, a prescription drug that could have serious health risks if used without medical supervision. Both products were being sold as dietary supplements, without a prescription, for increasing desire, confidence and sexual performance. **References:** 1. Medwatch Safety Alert, 4 April 2003 (http://www.fda.gov/medwatch/SAFETY/2003/vinarol.htm). 2. Medwatch Safety Alert, 23 May 2003 (http://www.fda.gov/medwatch/SAFETY/2003/vinarol.htm).

Product Name: Herbal Medicines

Country	Effective Date	Description of action taken Grounds for decision
New Zealand	2003	The Medicines Safety Authority of the Ministry of Health in New Zealand (Medsafe) has ordered the withdrawal of several traditional Chinese medicines sold as herbal remedies since they have been found to contain scheduled medicines and toxic substances. Products to be withdrawn include: • Guan Xin Su He capsules, Long Dan Xie Gan Wan Pills, Zhiyuan Xinqinkeli sachets – all containing aristolochic acid which has been linked to severe kidney damage and urinary tract cancer; • Wei Ge Wang tablets – containing prescription medicine sildenafil; • Sang Ju Gan Mao Pian tablets – containing pharmacy-only medicines diclofenac (a non-steroidal anti-inflammatory agent) and chlorpheniramine (an antihistamine); • Yen Qiao Jie Du Pian capsules – containing chlorpheniramine, diclofenac and paracetamol; • Niu Huang Jie Du Pian tablets – containing 4% arsenic; • Xiaoke Wan pills – containing glibenclamide, a prescription-only hypoglycaemic agent; • Shuen Feng cream – containing ketoconazole, a prescription antifungal agent; • Dezhong Rhinitis drops – containing ephedrine hydrochloride. **Reference:** Media Release, 21 January 2003 (http://www.medsafe.govt.nz).

Product Name: Non steroidal anti-inflammatory drugs (NSAIDs)

Country	Effective Date	Description of action taken Grounds for decision
USA	2005	The United States Food and Drug Administration (FDA) has asked manufacturers of all marketed prescription non steroidal anti-inflammatory drugs (NSAIDs), including celecoxib (Celebrex), a cyclooxygenase-2 selective NSAID, to revise the labelling (package insert) for their products to include a boxed warning and a Medication Guide. The boxed warning will highlight the potential for increased risk of cardiovascular events (CV) with these drugs and

		the well-described, serious, and potentially life-threatening gastrointestinal (GI) bleeding associated with their use. The Medication Guide will accompany every prescription NSAID at the time it is dispensed to better inform patients about the CV and GI risks. Finally, FDA has also asked manufacturers of non-prescription (OTC) NSAIDs to revise their labelling to include more specific information about the potential GI and CV risks, and information to assist consumers in the safe use of the drug. This announcement does not apply to aspirin as it has clearly been shown to reduce the risk of serious adverse CV events in certain patient populations. **Reference:** US FDA Public Health Advisory, 7 April 2005 (http://www.fda.gov).

Product Name: **Statins**

Country	Effective Date	Description of action taken Grounds for decision
Australia	2005	The pregnancy classification of the statins has been changed from category C to category D by the Australian Drug Evaluation Committee. The classification change for the statins, already contraindicated in pregnancy, comes after the publication of a series of cases of fetal malformation. Category D drugs are those "which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage" and may also have adverse pharmacological effects. **Reference:** Australian Adverse Drug Reactions Bulletin 24: 4, No. 1, February 2005.