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PHARMACEUTICALS: RESTRICTIONS IN USE AND AVAILABILITY

Essential Medicines and Pharmaceutical Policies
Quality Assurance and Safety: Medicines
Health Systems and Services

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"Consolidated List of Products whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments"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 Twelfth Issue - 2008

Essential Medicines and Pharmaceutical Policies
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This text is the update to the Twelfth Issue of the United Nations Consolidated List of Products whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments - Pharmaceuticals (UN General Assembly Resolutions 37/137, 1982; 38/149, 1983; 39/229, 1984; 44/226, 1989).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 October 2008.

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

While the information cannot be regarded as exhaustive, either in terms of products or regulatory measures, it covers regulatory actions taken by a total of 27 governments on 88 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 have been requested from governments; products which clearly do not meet the criteria have been omitted after consultation with governments. Information received from non-governmental organizations has, in each case, been verified with governments.

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

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Alphabetical listing

Monocomponent Products

Combination of Products

Group Products

Product Name: Acetylsalicylic acid

CAS number: 50-78-2

Other Names: 2-Acetoxybenzoic acid; Aspirin

Country	Effective Date	Description of action taken Grounds for decision
Serbia	May 2005	Due to risk of Reye's syndrome, all registered products containing acetylsalicylic acid are contraindicated in children under the age of 12 years and in women during lactation. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, March 2005.

Product Name: Alefacept

CAS number: 222535-22-0

Other Names: Amevive

Country	Effective Date	Description of action taken Grounds for decision
USA	November 2005	This recombinant human fusion protein is contraindicated in patients with HIV infection because it reduces CD4+ T lymphocyte counts which in turn can increase disease complications or accelerate disease progress in these patients. **Reference**: 1. Safety information from the U.S. Food and Drug Administration, 9 November 2005 (www.fda.gov). 2. WHO Pharmaceuticals Newsletter No. 5, 2005.

Product Name: Amlodipine

CAS number: 88150-42-9

Other Names: 3-Ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate monobenzenesulphonate

Country	Effective Date	Description of action taken Grounds for decision
Serbia	August 2006	All registered original and generic amlodipine containing products are contraindicated in patients with any of the following conditions: cardiogenic shock, clinically significant aortic stenosis, unstable angina pectoris (excluding Prinzmetal's angina), as well as during lactation. **Reference**: Communication from the National Pharmacovigilance

Centre of Serbia, July 2006.

Product Name: Aprotinin

CAS number: 9087-70-1

Other Names: Trasylol

Country	Effective Date	Description of action taken Grounds for decision
Worldwide		The manufacturer (Bayer Inc.) has been advised to suspend the marketing of this product because the risks from this medicine are greater than the benefits. **References**: 1. Press Release. European Medicines Agency, 21 November 2007 (www.emea.europa.en). 2. FDA News. U.S. Food and Drug Administration, 14 May 2008 (www.fda.gov).

Product Name: Astemizole

CAS number: 68844-77-9

Other Names: 1-(4-Fluorobenzyl)benzimidazol-2-yl[1-(4-methoxyphenethyl)-4-piperidyl] amine; Astezol, Astol

Country	Effective Date	Description of action taken Grounds for decision
Chile	24 November 2004	The import, distribution and sale of products containing astemizol have been banned due to cardiotoxic effects of these products. **Reference**: Resolución Nº 10228 de 24 de noviembre de 2004, la Dirección del Instituto de Salud Pública, Chile.

Product Name: Buflomedil

CAS number: 55837-25-7

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
France	2006	The French Regulatory Agency (AFSSAPS) has decided to withdraw buflomedil 300 mg tablets from the market and to strengthen the summary of product characteristics (SPC) for buflomedil 150mg. The Agency undertook a benefit-harm evaluation of buflomedil (used chiefly to treat peripheral vascular disease), following the results of two enquiries about cardiovascular and neurological toxicity in accidental or voluntary buflomedil overdoses. The Agency says that neurological and serious cardiac adverse events

	occurred within 15–90 minutes in cases of suicide with buflomedil and, because of a narrow therapeutic index, the clinical manifestations of buflomedil overdose are serious. The majority of voluntary overdose cases occurred with 300 mg dose of buflomedil. The Agency has decided to recall batches of buflomedil 300 mg tablets from the market, and to include the following information in the SPC for buflomedil 150 mg: • indicated for improvement of symptoms of peripheral occlusive arterial disorders or Raynaud's disease only; • contraindicated in patients with severe renal failure (creatinine clearance < 30 mL/min); • dose adaptation in patients with moderate renal failure (creatinine clearance between 30 and 90 mL/min) and low body weight (< 50 kg); • control of creatinine clearance before and during treatment; and • information about low therapeutic range of buflomedil. **Reference**: WHO Pharmaceuticals Newsletter No. 1, 2007.

Product Name: Cabergoline

CAS number: 81409-90-7

Other Names: Cabaser, Dostinex

Country	Effective Date	Description of action taken Grounds for decision
Japan	19 April 2007	The Ministry of Health, Labour and Welfare, Tokyo has instructed the company to update the package insert to contraindicate the use of this product in patients with valvular heart diseases, etc. **Reference**: Pharmaceuticals and Medical Devices Safety Information No. 237.

Product Name: Carbamazepine

CAS number: 298-46-4

Other Names: Tagretol

Country	Effective Date	Description of action taken Grounds for decision
USA	December 2007	The US FDA has modified the label to include a warning about the increase of risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis with this product in patients who are positive for the HLA-

		B*1502 allele. The allele occurs exclusively in patients with Asian ancestry. Screening for this allele should be performed in the patients and treatment with carbamazepine should not be started in those testing positive for the allele. **References**: 1. FDA Alert. U.S. Food and Drug Administration, 12 December 2007 (www.fda.gov). 2. WHO Pharmaceuticals Newsletter No.1, 2008.

Product Name: Ceftriaxone

CAS number: 73384-59-5

Other Names: Rocephin

Country	Effective Date	Description of action taken Grounds for decision
USA	June 2007	The US FDA advises that hyperbilirubinaemic neonates, especially those who are premature, should not receive ceftriaxone. This action is based on reports of death of neonates worldwide associated with calcium-ceftriaxone precipitates in the lungs and kidneys of these infants. **References**: 1. 'Dear Health-care Professional' letter from Roche Laboratories Inc., June 2007 (www.fda.gov). 2. WHO Pharmaceuticals Newsletter No. 4, 2007.

Product Name: Cinacalcet

CAS number: 226256-56-0

Other Names: Sensipar

Country	Effective Date	Description of action taken Grounds for decision
Canada	June 2007	Cinacalcet (Sensipar) is no longer indicated in the treatment of secondary hyperparathyroidism in chronic kidney disease (CKD) patients who are *not* receiving dialysis. The use is now restricted for the treatment of secondary hyperparathyroidism in patients with CKD who are receiving dialysis. This restriction follows study results involving cinacalcet recipients with secondary hyperparathyroidism and CKD which showed that cinacalcept recipients not receiving dialysis were more likely to develop serum calcium levels below the lower limit of the normal range (8.4 mg/dL) compared with those receiving dialysis. **Reference**: 'Dear Health-care Professional' letter from Amgen Canada Inc., 9 June 2007 (www.hc-gc.sc.ca).

Product Name: Cisapride

CAS number: 81098-60-4

Other Names: 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
Serbia	August 2005	Cisapride injections have been withdrawn due to concerns about life-threatening cardiac arrhythmias. This measure follows actions previously taken worldwide. The use of cisapride tablets has been restricted to treatment of acute and severe exacerbations of chronic idiopathic or diabetic gastroparesis in adults who are refractory to other therapy. Administration in hospital environment accompanied with cardiologic monitoring is required. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, May 2005.

Product Name: Clobutinol

CAS number: 14860-49-2

Other Names: Silomat

Country	Effective Date	Description of action taken Grounds for decision
Argentina	4 September 2007	All products containing clobutinol have been withdrawn. **Reference**: Communication from the National Pharmacovigilance Centre of Argentina, 4 September 2007.

Product Name: Codeine

CAS number: 76-57-3

Other Names: Methylmorphine

Country	Effective Date	Description of action taken Grounds for decision
Sweden	December 2006	The Swedish Medical Products Agency (MPA) has warned that, breastfeeding mothers receiving codeine should use the lowest dose possible and monitor their

		infant for signs of overdose such as breathing difficulties, difficulty in breastfeeding, drowsiness or listlessness, flaccidity and small pupils; should any of these signs be noted, medical care should immediately be sought. This warning has been issued because in rare cases, codeine in normal doses given to breastfeeding mothers can lead to dangerously high amounts of morphine being delivered to the infant. Codeine is converted to morphine in the body. In rare cases in nursing mothers who are ultra-rapid metabolizers of codeine, a very high dose of morphine could get delivered to the child through the mother's milk, with serious adverse results. **References**: 1. Swedish Medical Products Agency, December 2006 (www.lakemedelsverket.se). 2. WHO Pharmaceuticals Newsletter No. 2, 2007.

Product Name: Desmopressin nasal spray

CAS number: 16679-58-6

Other Names: Desmospray

Country	Effective Date	Description of action taken Grounds for decision
UK	April 2007	Desmopressin nasal spray products are no longer indicated in Primary Nocturnal Enuresis (PNE) (bedwetting). This measure was implemented by the UK Medicines and Healthcare products Regulatory Agency (MHRA) because the nasal formulations were associated with a majority of the adverse drug reactions occurring in PNE patients while the oral formulations had a more favourable risk-benefit profile. Rare, serious adverse reactions associated with nasal desmopressin included hyponatraemia, seizures and water intoxication. (Nasal desmopressin is still approved in cranial diabetes insipidus and multiple sclerosis-related nocturia). **References**: 1. Letter to health-care providers from MHRA, 18 April 2007 (www.mhra.gov.uk). 2. WHO Pharmaceuticals Newsletter No. 3, 2007.

Product Name: Dolasetron

CAS number: 115956-12-2

Other Names: Anzemet

Country	Effective Date	Description of action taken Grounds for decision
Canada	June 2006	This product is contraindicated in patients below 18 years of age. In addition the product is not to be used to manage postoperative nausea and vomiting. These actions follow reports of myocardial infarction, sustained arrhythmias, and one fatal cardiac arrest associated with the use of dolasetron (Anzemet) in children and adolescents, and because there is an unfavourable risk/benefit ratio for postoperative use of the drug in patients aged ≥ 18 years. **References**: 1. Advisories, Warnings and Recalls. Health Canada, 23 June 2006 (www.hc-sc.gc.ca). 2. WHO Pharmaceuticals Newsletter No. 4, 2006.

Product Name: Ephedrine

CAS number: 299-42-3

Other Names: Ephedrinum

Country	Effective Date	Description of action taken Grounds for decision
Democratic Republic of Timor-Leste	2005	To be removed from market. Not safe for use in asthma. **Reference**: SEMWE Farmacia Report, 6 April 2005.

Product Name: Ergometrine

CAS number: 60-97-7

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Democratic Republic of Timor-Leste	2005	Tablets to be removed from the market because tablets are unstable in tropical countries under high temperature and humidity. Only the injection will be available. **Reference**: SEMWE Farmacia Report, 6 April 2005.

Product Name: Gatifloxacin

CAS number: 160738-57-8

Other Names: 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylpiperazin-1-yl)-4-oxo-quinoline-3-carboxylic acid

Country	Effective Date	Description of action taken Grounds for decision
Malaysia	May 2006	Products containing gatifloxacin will not be registered since they are contraindicated in diabetic patients and due to cases of serious hypo-and hyperglycaemia that have been reported worldwide in patients receiving gatifloxacin. **Reference**: Communication from the Malaysian National Pharmacovigilance Centre, 2007.
Brazil	March 2006	Severely restricted use due to risks of hypo- and hyperglycaemic events. **Reference**: 1. Communication from the Brazilian Pharmacovigilance Office, Brazilian Health Surveillance Agency (ANVISA), 5 September 2007 (www.anvisa.gov.br).

Product Name: Glucosamine

CAS number: 3416-24-8

Other Names: 2-Amino-2-deoxy-β-D-glucopyranose

Country	Effective Date	Description of action taken Grounds for decision
Malaysia	December 2005	To include the statement “Derived from seafood” for products containing glucosamine and chitin. But this statement does not apply to products where the source is clearly from seafood. **Reference**: Communication from the Malaysian Pharmacovigilance Centre, 2007.

Product Name: Hydromorphone hydrochloride

CAS number: 71-68-1

Other Names: Palladone

Country	Effective Date	Description of action taken Grounds for decision
USA	July 2005	The US FDA has recommended suspending the sales and marketing of hydromorphone hydrochloride (Palladone) controlled-release capsules in the USA, as

		co-ingestion of the drug with alcohol may cause severe adverse effects, such as depressed breathing, coma and even death. **References**: 1. FDA News.U.S. Food and Drug Administration, 13 July 2005 (www.fda.gov). 2. WHO Pharmaceuticals Newsletter No. 3, 2005**.**
Switzerland	2005	Withdrawn due to potential to cause life threatening respiratory depression. **Reference**: Communication from Swissmedic, 2007.

Product Name: Interferon-gamma-1b

CAS number: 98059-61-1

Other Names: Actimmune

Country	Effective Date	Description of action taken Grounds for decision
USA	March 2007	The U.S. FDA states that interferon-gamma-1b (IFN-γ-1b) (Actimmune) is not approved for the treatment of idiopathic pulmonary fibrosis, IPF. An interim analysis of the international study of survival outcome in IPF of IFN- γ-1b showed that IFN- γ-1b recipients did not benefit from the drug. Compared with 12.7% deaths in the placebo group, 14.5% of patients died in the IFN-γ-1b group. **References**: 1. Public Health Advisory. U.S. Food and Drug Administration, 9 March 2007 (www.fda.gov). 2. WHO Pharmaceuticals Newsletter No. 2, 2007.

Product Name: Isotretinoin

CAS number: 4759-48-2

Other Names: Accutane

Country	Effective Date	Description of action taken Grounds for decision
Chile	30 December 2005	Indication limited to oral or topical use, and only in the treatment of severe acne that does not respond to other treatments; not to be used during pregnancy and during lactation. The package insert should warn about the teratogenic potential and suicidal ideation associated with this product. **Reference**: Resolución Nº 12359 de 30 de diciembre de 2005, la Dirección del Instituto, de Salud Pública, Chile.

USA	August 2005	The U.S. FDA has approved a strengthened isotretinoin (Accutane and generics) risk management programme (iPLEDGE) in an effort to prevent use of the drug during pregnancy. Prescribers, pharmacies, wholesalers and patients, who agree to accept specific responsibilities, will be required to register in iPLEDGE before receiving authorization to prescribe, dispense, distribute or obtain isotretinoin. The responsibilities are designed to reduce the risk of exposure to isotretinoin during pregnancy since exposure to isotretinoin during pregnancy may significantly increase the risk of congenital disorders. From 1 November 2005, only iPLEDGE-registered wholesalers will be able to obtain isotretinoin from the manufacturers and only iPLEDGE-registered pharmacies will be able to receive isotretinoin from registered wholesalers. From 31 December 2005, pharmacies will be required to receive iPLEDGE authorization before dispensing an isotretinoin prescription, and only prescriptions from registered prescribers for registered patients will be accepted. **References**: 1. Public Health Advisory. U.S. Food and Drug Administration, 12 August 2005 (www.fda.gov). 2. Press Release. U.S. Food and Drug Administration, 12 August 2005 (www.fda.gov).

Product Name: Ketamine

CAS number: 6740-88-1

Other Names: Ketamini hydrochloidum

Country	Effective Date	Description of action taken Grounds for decision
UK	January 2006	As of 1 January 2006, ketamine has become a controlled drug, under the Misuse of Drugs Act. It is now a Class C drug, in Schedule 4 part 1, which puts it in the same category as a majority of the benzodiazepines such as diazepam. This step has been taken because of its increasing misuse. **Reference**: WHO Pharmaceuticals Newsletter No. 1, 2006.

Product Name: Ketoconazole

CAS number: 65277-42-1

Other Names: (±)-cis-1-Acetyl-4-{p-[2-(2,4-dichlorophenyl)-2-imidazol-1-ylmethyl-1,3-dioxolan-4-ylmethoxy]phenyl}piperazine; Nizoral

Country	Effective Date	Description of action taken Grounds for decision
UK	March 2008	Several therapeutic indications were removed due to the risk of serious hepatotoxicity. The Medicines and Heathcare prodcuts Regulatory Agency (MHRA) advises that oral ketoconazole should only be used for malassezia folliculitis, dermatophytosis and chronic candidosis, which cannot be treated topically. Ketoconazole should only be used in patients with infections resistant to fluconazole, terbinafine or itraconazole, or in patients who are intolerant to these drugs. **Reference**: Drug Safety Update, Vol. 1 (8), 2 March 2008 (www.mhra.gov.uk).

Product Name: Lamotrigine

CAS number: 84057-84-1

Other Names: 6-(2,3-Dichlorophenyl)-1,2,4-triazine-3,5-diamine

Country	Effective Date	Description of action taken Grounds for decision
Serbia	March 2007	Due to risk of cleft lip and/or palate in neonates associated with mother's use of lamotrigine during first trimester of pregnancy. If therapy with lamotrigine is necessary during pregnancy, if the lowest possible dose should be used. This measure refers to all registered original and generic products containing lamotrigine. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, October 2006.

Product Name: l-arginine

CAS number: 74-79-3

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Canada	May 2006	Use contraindicated in patients who have previously had a heart attack (1) since a recent study published in the Journal of the American Medical Association in

		January 2006 suggests that l-arginine may not help improve heart and circulatory function following a first heart attack and may be associated with an increased risk of death when used after a heart attack (2). All l-arginine products are now required to carry a warning on their label reflecting this recent scientific information. **References**: 1. Advisory Health Canada, 16 May 2006 (www.he-sc.gc.ca). 2. Schulman SP et al. l-Arginine therapy in acute myocardial infarction. The Journal of the American Medical Association, 295: 58-64, 2006.
Malaysia	September 2006	The following warning must be included on labels and package inserts of oral health supplement products containing l-arginine: "Arginine is not recommended for patients following a heart attack". This recommendation follows similar measures taken in Canada. **Reference**: Communication from the Malaysian National Pharmacovigilance Centre, 2007.

Product Name: Lidocaine

CAS number: 137-58-6

Other Names: 2-(diethylamino)-N-(2,6-dimethylphenyl) acetamide; Lignocaine

Country	Effective Date	Description of action taken Grounds for decision
Serbia	December 2005	Not to be used in children under the age of 12 years due to risk of lidocaine overdosage with nervous and cardiovascular system toxicity. This measure refers to all registered original and generic lidocaine containing products intended for local administration. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, October 2005.

Product Name: Lindane

CAS number: 58-89-9

Other Names: (1α,2α,3β,4α,5α,6β-)Hexachlorocyclohexane; Gamex

Country	Effective Date	Description of action taken Grounds for decision

Serbia	August 2006	The use of all products containing lindane has been restricted to treatments only when response to other pediculocides and scabicides is inadequate, while contraindicated in neonates and infants. Precaution is required for use in children with low body weight or in children predisposed to convulsions. Application in thin layer on dry and intact skin using protective gloves is recommended. Medical advice is required for repeated administration. New findings of neurological side effects led to these measures. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, June 2006.

Product Name: Lumiracoxib

CAS number: 220991-20-8

Other Names: {2-[(2-chloro-6-fluorophenyl)amino]-5-methylphenyl}acetic acid; Prexige

Country	Effective Date	Description of action taken Grounds for decision
Australia	August 2007	Australia's Therapeutic Goods Administration (TGA) cancelled the registration of lumiracoxib due to reports of serious liver adverse effects associated with the use of the drug. **References**: 1. Media Statement. Therapeutics Goods Administration, 11 August 2007 (www.tga.gov.au). 2. WHO Pharmaceuticals Newsletter No. 5, 2007.
Canada	October 2007	Health Canada has requested that Novartis stop the sale of lumiracoxib in Canada. This action follows Health Canada's review of all safety and efficacy data for lumiracoxib and it's conclusion that the risk of serious hepatotoxicity associated with the use of lumiracoxib cannot be safely and effectively managed. **Reference**: WHO Pharmaceuticals Newsletter No. 5, 2007.
Europe	13 December 2007	Following the suspension of lumiracoxib licences in the UK (19 November 2007), and similar action in some other countries, because of concerns over liver side effects, EMEA has recommended the withdrawal of lumiracoxib across all Member States,. **Reference**: Press Release. EMEA, 13 December 2007 (www.emea.europa.eu).

New Zealand	2007	Withdrawn from the New Zealand market due to the risk of liver damage associated with prolonged use of low-dose lumiracoxib. **Reference**: WHO Pharmaceuticals Newsletter No.1, 2008.
Republic of Turkey	15 August 2007	Turkey has withdrawn the marketing authorization for 100 mg lumiracoxib tablets due to case of serious liver adverse effects reported in Australia. **Reference**: 1. WHO Pharmaceuticals Newsletter No. 5, 2007. 2. Communication from the Turkish Pharmacovigilance Centre (TUFAM), Ministry of Health, Republic of Turkey.

Product Name: Meloxicam

CAS number: 71125-38-7

Other Names: Melox

Country	Effective Date	Description of action taken Grounds for decision
Serbia	February 2006	Use of meloxicam is contraindicated in patients with gastrointestinal bleeding, recent cerebrovascular bleeding or other bleeding disorders, and in patients with severe uncontrolled heart failure. Warning has been issued regarding risk of masking symptoms of infectious disease by use of meloxicam, as well as interaction with angiotensin II receptor antagonists and Angiotensin Converting Enzyme (ACE) inhibitors leading to acute renal failure. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, December 2005.

Product Name: Meprobamate

CAS number: 57-53-4

Other Names:; Equanil

Country	Effective Date	Description of action taken Grounds for decision
UK	February 2008	The MHRA is advising health-care professionals that treatment with meprobamate should not be initiated due to risks of dependence, withdrawal, abuse and other unpleasant adverse effects. **Reference**: Drug Safety Update, Vol. 1 (7): 5 February 2008 (www.mhra.gov.uk).

Product Name: Metamizole sodium

CAS number: 68-89-3

Other Names: Dipyrone; Methanesulfonic acid; Analgin

Country	Effective Date	Description of action taken Grounds for decision
Democratic Republic of Timor-Leste	2005	To be removed due to reports of agranulocytosis. **Reference:** SEMWE Farmacia Report, 6 April 2005.
France	18 July 2006	Dipyone/metamizole/noramidopyrin containing products are no longer marketed du to negative benefit/risk evaluation. **Reference**: Communication from AFSSAPS, 3 August 2006.
Nigeria	2005	In view of recorded cases of adverse reactions the National Agency for Food and Drug Administration & Control (NAFDAC) has warned against the use of all brands of dipyrone drugs (Novalgin, Analgin, Optalgin, Drunalgin, Dr. Meyers Novalmin, Akarin, etc). With effect from 1 September 2005, the Agency will not allow the manufacture and importation of these drugs in any dosage form (injections, tablets and syrups) into the country. Also, with effect from 1st January, 2006, the sale and use of all brands of matamizole drugs are banned. **References**: 1. Communication from the Nigerian Pharmacovigilance Centre, 27 July 2007 2. Knowledge Base, NAFDAC, 4 December 2007 (www.nafdacnigeria.net)
Serbia	May 2005	The labels of all registered products containing metamizole are required to include the boxed warning: “The use is not recommended in children and adolescents under the age of 18 years.” The use of products containing metamizole has been restricted to short-term treatment of severe post-traumatic and post-surgical pains where other non-opioid analgesics show ineffectiveness. These measures are based on postmarketing reports of agranulocytosis (including one case with fatal outcome) associated with the use of metamizole, regulatory measures taken worldwide, and relevant medical literature. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, March 2005.

Product Name: Metoclopramide

CAS number: 364-62-5

Other Names: Primperan, Reglan

Country	Effective Date	Description of action taken Grounds for decision
The Netherlands	February 2007	Following an increase in the number of registered cases of extrapyramidal symptoms in children receiving metoclopramide, the Medicines Evaluation Board (MEB) in the Netherlands has restricted the use of metoclopramide in this population. The Board says metoclopramide should be used only in the treatment of severe nausea and vomiting of known origin, and only if treatment with other products is ineffective or is not possible. **Reference**: WHO Pharmaceuticals Newsletter No. 2, 2007.

Product Name: Natalizumab

CAS number: 189261-10-7

Other Names: Tysabri

Country	Effective Date	Description of action taken Grounds for decision
USA	July 2006	The US FDA has reintroduced natalizumab as monotherapy for patients with relapsing forms of multiple sclerosis (MS) under a restricted distribution/risk management plan. Previously the companies concerned had voluntarily suspended natalizumab (Tysabri) from the US market due to reports of progressive multifocal leukoencephalopathy (PML). Natalizumab (Tysabri) will now be available only through a special restricted distribution and risk management program called the Tysabri Outreach: Unified Commitment to Health (TOUCH) Prescribing Program. The TOUCH Program was developed to ensure the proper use of natalizumab (Tysabri) and to evaluate the PML incidence, PML risk factors and other serious opportunistic infections associated with the drug. **Reference**: WHO Pharmaceuticals Newsletter No. 4, 2006.

Product Name: Nevirapine

CAS number: 129618-40-2

Other Names: 11-cyclopropyl-5, 11-dihydro-4-methyl-6h-dipyrido [3, 2-b: 2', 3'-e] [1, 4] diazepin-6-one;Viramune

Country	Effective Date	Description of action taken Grounds for decision
Brazil	June 2007	Withdrawn by manufacturer. **References**: Communication from the Brazilian Pharmacovigilance Office, Brazilian Health Surveillance Agency (ANVISA), 5 September 2007 (www.anvisa.gov.br)
Malaysia	March 2005	Restriction of indication for product containing nevirapine due to risk of serious liver toxicity in patients with high CD4+ cell counts. The indication is restricted as follows:- • Indications and Usage section of the product label now recommends against starting nevirapine treatment in women with CD4+ cell counts greater than 250 cells/mm3 unless benefits clearly outweigh risks. **Reference**: Communication from the Malaysian National Pharmacovigilance Centre, 2007.

Product Name: Nimesulide

CAS number: 51803-78-2

Other Names: Nimulid, Aulin, Mesulid, Mesine

Country	Effective Date	Description of action taken Grounds for decision
Chile	24 November 2004	Products containing more than 100 mg of nimesulide (active principle) may not be used in paeditric population. According to the Dirección del Instituto de Salud Pública, there is insufficient scientific evidence to support the safety of a dose of > 100 mg nimesulide in this population. **Reference:** Resolución Nº 10228 de 24 de noviembre de 2004, la Dirección del Instituto de Salud Pública, Chile.
Europe	21 September 2007	In order to minimize the risk of liver injury, the Committee for Medicinal Products for Human Use (CHMP) has recommended that treatment with nimesulide should be restricted to a maximum of 15 days and that consequently all packs of nimesulide containing more than 30 doses (tablets or sachets) should be removed from the market.

		Reference: Press Release. EMEA, 21 September 2007 (www.emea.europa.eu).
Ghana	August 2007	The National Regulatory Agency (NRA) suspended the marketing authorization for nimesulide-containing products; a 'Dear Health-care Professional' letter was also issued based on the WHO Drug Alert No. 113 that highlighted the decision in the Republic of Ireland to withdraw these products from the Irish market. **Reference**: Communication from the Food & Drugs Board, Ghana, 1 December 2008.
Nigeria	2005	Nimesulide containing products banned due to adverse health effects. **Reference**: 1. Communication from the Nigerian Pharmacovigilance Centre, 27 July 2007. 2. Sanctions, NAFDAC, 8 Novmber 2007 (www.nafdacnigeria.net).
Republic of Ireland	May 2007	The Irish Medicines Board (IMB) has announced the suspension of the marketing and sale of nimesulide-containing medicinal products for oral use available in Ireland. The suspended products include Aulin (100 mg tablets and granules), Mesulid (100 mg tablets and granules) and Mesine (100 mg tablets). The IMB decision was based on new information from a National Liver Transplant Unit that six patients required liver transplant following treatment with nimesulide. The IMB has received 53 liver-related adverse reaction reports with nimesulide since the product was first approved for use in Ireland in 1995. **References**: 1. Press Release from the Irish Medicines Board, 15 May 2007 (www.imb.ie). 2. Alert No. 113, Information Exchange System, WHO, 23 May 2007 (www.who.int/medicines). 3. WHO Pharmaceuticals Newsletter No. 3, 2007.
Serbia	November 2005	The use of all registered products containing nimesulide for systemic administration has been restricted to treatment of acute pain, symptomatic treatment of osteoarthritis and primary dysmenorrhea, and contraindicated in children under the age of 12 years, in patients with active peptic ulcer, hepatic disease or serious renal impairment, as well as in hypersensitive patients. Concomitant use with potential hepatotoxic drugs, other non-steroidal anti-inflammatory drugs (NSAID) and alcohol are not recommended. These measures are based on findings of increased risk of hepatotoxicity and nephrotoxicity with

		nimesulide. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, October 2007**.**
Ukraine	July 2007	Use of nimesulide-containing medicinal products in children under 12 years of age is banned. **Reference**: Information provided by the National Pharmacovigilance Centre, Ukraine, 2007.

Product Name: Nitrofural

CAS number: 59-87-0

Other Names: Nitrofurazone

Country	Effective Date	Description of action taken Grounds for decision
Armenia	2006	Scientific Centre of Drug and Medical Technology Expertise Ministry of Health (SCDMTE MoH) has withdrawn the use of nitrofurazone tablets. Nitrofurazone was approved only for external application, for the topical treatment of various skin conditions. Following findings of *in vitro* mutagenicity and carcinogenicity, the use of topical preparations containing nitrofurazone was restricted in several countries. **Reference**: Communication from the Armenian Drug Regulatory Authority, 2007.

Product Name: Parecoxib

CAS number: 202409-33-4

Other Names: Dynastat

Country	Effective Date	Description of action taken Grounds for decision
Chile	17 December 2004	Because of severe risk of adverse reactions, use not recommended in pain related to coronary bypass surgery. **Reference:** Communication from Chile Pharmacovigilance Centre, 2007.
Malaysia	August 2005	Following a review of the appeal submitted by Pfizer (M), the Malaysian Regulatory Authority has decided to reinstate the registration for intravenous (IV) parecoxib (Inj Dynastat) but with the following conditions: • Indication: Restricted to the management of

		postoperative pain in the immediate postoperative setting only. • Use limited to two days only with a maximum dose of 80 mg. **Reference**: Communication from the Malaysian National Pharmacovigilance Centre, 2007.

Product Name: Pemoline

CAS number: 2152-34-3

Other Names: Cylert

Country	Effective Date	Description of action taken Grounds for decision
USA	October 2005	Withdrawn due to risk of liver toxicity. The US FDA has concluded that the overall risk of liver toxicity from pemoline (Cylert) outweighs the benefits of this drug indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). US FDA is aware of 13 reports of liver failure resulting in liver transplant or death associated with pemoline use. The manufacturer (Abbott) of the proprietary version (Cylert) of the product discontinued its sales in May 2005. Subsequently, manufacturers of the generic versions also stopped sales and marketing of all generic pemoline products. **Reference**: Alert. U.S. Food and Drug Administration, October 2005 (www.fda.gov).

Product Name: Pergolide

CAS number: 66104-22-1

Other Names: Permax

Country	Effective Date	Description of action taken Grounds for decision
Canada	30 August 2007	Sales of pergolide products (Permax) have ceased in Canada as of 30 August 2007 because of further evidence of valvulopathy associated with its use. **Reference**: WHO Pharmaceuticals Newsletter No. 5, 2007.
Japan	April 2007	Contraindicated in patients with valvular disease. Package insert updated. **Reference**: Pharmaceutical and Medical Devices Safety Information No. 237.

USA	March 2007	Removed from the market due to the risk of serious damage to the heart valves of patients treated with these products. The US FDA notes that new studies confirm old data associating pergolide with increased chance of regurgitation (back-flow of blood) of the mitral, tricuspid and aortic valves of the heart. The Agency advises that the products being removed include two generic versions of pergolide manufactured by Par and Teca and a proprietary version (Permax) manufactured by Valeant Pharmaceuticals. **Reference**: WHO Pharmaceuticals Newsletter No. 2, 2007.

Product Name: Phenylpropanolamine

Suspended while adverse reaction reports are reviewed

CAS number: 14838-15-4

Other Names: (+/-) norephedrine

Country	Effective Date	Description of action taken Grounds for decision
Cameroon	2000	All phenylpropanolamine (PPA)-containing products are banned and no longer marketed. **Reference:** Communication from Cameroon Pharmacovigilance Centre, 24 July 2007.
Democratic Republic of Timor-Leste	2005	PPA products to be gradually removed from the market due to risk of haemorrhagic stroke. **Reference:** SEMWE Farmacia Report, 6 April 2005.
Portugal	2005	The Portuguese regulatory body, Infarmed, has suspended cold and flu products containing the decongestant PPA, while it reviews PPA's risk/benefit profile following worldwide concerns of cerebral haemorrhage and other adverse reactions. **Reference**: Boletim de Farmaco Vigilancia, 9 (2), 2005.
Nigeria	2004	All preparations containing PPA are banned. **Reference**: Communication from NAFDAC, 13 September 2007.

Product Name: Piroxicam

CAS number: 36322-90-4

Other Names: **Feldene; Brexidol**

Country	Effective Date	Description of action taken Grounds for decision
Europe	June 2007	The EMEA has recommended restrictions on the use of piroxicam-containing medicinal products because of the risk of gastrointestinal side effects and serious skin reactions. The Agency advises that piroxicam should no longer be used for short-term painful and inflammatory conditions, can be prescribed to relieve the symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, but should not be used as a first-line treatment for these disorders. Treatment should be reviewed after 14 days. **References**: 1. Press Release. EMEA, 25 June 2007 (www.emea.europa.eu). 2. WHO Pharmaceuticals Newsletter No. 4, 2007.
Serbia	July 2007	Not indicated for acute pain and inflammatory conditions. The use has been restricted to second-line therapy for symptomatic treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis. Lowest effective dose (up to 20 mg daily) and use for shortest time period as possible are recommended. Contraindicated in patients considered to be at high risk of side effects, as well as in patients who already take NSAID or anticoagulant therapy. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, June 2007.

Product Name: Promethazine

CAS number: 60-87-7

Other Names: Phenergan; Avomine

Country	Effective Date	Description of action taken Grounds for decision
Malaysia	May 2006	The following warning statement should be included in the package inserts of all products containing promethazine hydrochloride: • "It (brand or generic versions) should not be used in paediatric patients less than two years of age because of the potential for fatal respiratory depression". **Reference**:

		Communication from the Malaysian National Pharmacovigilance Centre, 2007.
Serbia	May 2005	The new contraindication and box warning are required to be labelled: “Not to be used in children under the age of two years.” Caution is required for use in children over two years of age; the lowest effective dose should be administered, and combination with drugs associated with depression of respiratory function should be avoided. These measures refer to oral dosage forms of promethazine. The measures are based on new findings of risk of fatal respiratory depression and apnea in paediatric population. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, March 2005.

Product Name: Pseudoephedrine

CAS number: 90-82-4

Other Names: (+)-(1S,2S)-2-Methylamino-1-phenylpropan-1-ol;

Country	Effective Date	Description of action taken Grounds for decision
Serbia	September 2006	All registered oral products containing pseudoephedrine which do not provide reliable dosing in children aged 2-6 years are contraindicated in children under the age of six years. All registered oral products containing pseudoephedrine which provide reliable dosing in children aged 2-6 years are contraindicated in children under the age of two years. Dosage was revised: 15 mg, 3 times daily in children aged 2-6 years; 30 mg, 3 times daily in children aged 6-12 years, 60 mg, 3 times daily in children aged 12-18 years. Administration restricted up to 5 days. Risk of pseudoephedrine related toxicity due to overdose led to these measures. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, March 2006.

Product Name: Quinine

CAS number: 130-95-0

Other Names:

Country	Effective Date	Description of action taken Grounds for decision

New Zealand	2007	Medsafe (Medicines and Medical Devices Safety Authority) under advice from the Medicines Adverse Reactions Committee (MARC) in New Zealand has ruled that quinine should no longer be used in treating nocturnal leg cramps. According to MARC, there is no evidence of efficacy of quinine for leg cramps, however there is sufficient evidence of harm due to unpredictable and potentially life threatening thrombocytopenia due to quinine. **Reference**: Prescriber Update Articles, 28 (1), November 2007.

Product Name: Rimonabant

CAS number: 168273-06-1

Other Names: Acomplia

Country	Effective Date	Description of action taken Grounds for decision
Europe	2008	The EMEA has suspended the marketing authorization for rimonabant (Acomplia) based on evidence that suggest serious psychiatric side effects associated with this product use. **References**: 1. Press Release. EMEA, 23 October 2008 (www.emea.europa.eu). 2. Alert No. 119, Information Exchange System, WHO, 25 October 2008 (www.who.int/medicines).

Product Name: Rofecoxib

CAS number: 162011-90-7

Other Names: 4-[p-(Methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone; Vioxx; Coxxil

Country	Effective Date	Description of action taken Grounds for decision
Chile	17 January 2005	Marketing authorization of products containing rofecoxib has been suspended due to adverse cardiovascular events associated with the drug in a clinical trial. **Reference:** Resolución Nº 168 de 17 de enero de 2005, la Dirección del Instituto de Salud Pública, Chile.

Product Name: Rosiglitazone

CAS number: 122320-73-4

Other Names: (±)-5-{p-[2-(Methyl-2-pyridylamino)ethoxy]benzyl}-2,4-thiazolidinedione; Avandia

Country	Effective Date	Description of action taken Grounds for decision
Australia		The Adverse Drug Reactions Advisory Committee (ADRAC) is warning that rosiglitazone and its combinations are contraindicated in the New York Heart Association (NYHA) heart failure Grades 3 and 4 and are only to be used with caution in Grades 1 and 2. A boxed warning states: "The use of rosiglitazone (AVANDIA/AVANDAMET) is not recommended in patients with known ischaemic heart disease, particularly in those taking nitrates. AVANDIA/AVANDAMET has been shown to be associated with an increased risk of myocardial ischaemia (angina, infarction) in pooled short-term clinical studies, particularly in those who needed several antidiabetic drugs or nitrates. **Reference**: Australian Adverse Drug Reactions Bulletin, Vol. 26 (6), 2007.
Canada		Due to reasons of cardiac safety, rosiglitazone (AVANDIA®) is no longer approved as monotherapy for type 2 diabetes, except when metformin use is contraindicated or not tolerated; rosiglitazone is no longer approved for use in combination with a sulfonylurea, except when metformin is contraindicated or not tolerated; treatment with all rosiglitazone products is now contraindicated in patients with any stage of heart failure (i.e., NYHA Class I, II, III or IV); rosiglitazone is not indicated for use with insulin since this combination is associated with an increased risk of heart failure. Rosiglitazone is not indicated for triple therapy (i.e., therapy with rosiglitazone in combination with both metformin and a sulfonylurea). Increases in congestive heart failure and other fluid retention-related events have been reported in patients receiving rosiglitazone as part of triple therapy. **Reference**: WHO Pharmaceuticals Newsletter No. 4, 2007.
Europe	January 2008	The EMEA has recommended updating the product information for rosiglitazone-containing antidiabetic medicines with the following: - a new warning that the use of rosiglitazone in patients with ischaemic heart disease and/or peripheral arterial disease is not recommended; - a new contraindication stating that rosiglitazone must not be used in patients with an acute coronary

		syndrome, such as angina or some types of myocardial infarction. **References**: 1. Press Release. EMEA, 24 January 2008 (www.emea.europa.eu). 2. WHO Pharmaceuticals Newsletter No.1, 2008.

Product Name: Sargramostim

CAS number: 123774-72-1

Other Names: Leukine

Country	Effective Date	Description of action taken Grounds for decision
USA	January 2008	The liquid formulation of sargramostim has been withdrawn due to an increase in adverse reaction reports since the liquid formulation was changed to include edetate disodium (EDTA). **References**: 1. 'Dear Health-care Professional' letter from Bayer HealthCare Pharmaceuticals, 23 January 2008 (www.fda.gov). 2. WHO Pharmaceuticals Newsletter No. 1, 2008.

Product Name: Sulfanilamide

CAS number: 63-74-1

Other Names: Streptocidum

Country	Effective Date	Description of action taken Grounds for decision
Armenia	2006	The Scientific Centre of Drug and Medical Technology Expertise, Ministry of Health (SCDMTE MoH) has decided not to approve the marketing of sulfanilamide because of increasing bacterial resistance and due to the availability of other antibiotics. **Reference**: Communication from the Armenian Drug Regulatory Authority, 2007.

Product Name: Technetium (99mTc) fanolesomab

CAS number:

Other Names: Neutrospec

Country	Effective Date	Description of action taken Grounds for decision
USA	December 2005	Voluntary suspension by manufacturer due to serious safety concerns. Technetium (99m Tc) fanolesomab

		(NeutroSpec) is indicated for radiologic imaging of patients with unclear signs and symptoms of appendicitis who are five years of age and older. There were reports of two deaths and 15 additional life-threatening adverse events in patients receiving technetium (99m Tc) fanolesomab (NeutroSpec). These events occurred within minutes of administration of Technetium (99m Tc) fanolesomab (NeutroSpec) and included shortness of breath, low blood pressure, and cardiopulmonary arrest. A review of all postmarketing reports showed an additional 46 patients who experienced adverse events that were similar but less severe. **References**: 1. Public Health Advisory. U.S. Food and Drug Administration, 19 December 2005 (www.fda.gov). 2. WHO Pharmaceuticals Newsletter No.1, 2006.

Product Name: Tegaserod

CAS number: 145158-71-0

Other Names: Zelmac, Zelnorm

Country	Effective Date	Description of action taken Grounds for decision
Argentina	15 June 2007	Suspended due to reports of adverse cardiovascular events. **Reference:** Communicado de Prensa, ANMAT, 1 June 2007.
Australia	4 April 2007	Recalled from the market because a recent retrospective analysis of pooled clinical trial data showed that the incidence of cardiovascular ischaemic events in patients taking tegaserod was higher than in those taking placebo. **Reference**: Product Recalls Therapeutic Goods Administration, 2007 (www.tga.gov.au).
Brazil	April 2007	Severely restricted use, change in package insert information (of Zelmac®) restricting its use for “women with diagnosis of irritable bowel syndrome, up to 55 years-old, without known cardiovascular illnesses or risk factors for them”. **Reference**: Communication from the Brazilian Pharmacovigilance Office, Brazilian Health Surveillance Agency (ANVISA), 5 September 2007.

China	June 2007	The production, sale and use of tegaserod (Zelnorm) have been suspended by the Chinese State Food and Drug Administration (SFDA) because the drug has been associated with an increased risk of strokes and heart attacks. **Reference**: WHO Pharmaceuticals Newsletter No. 4, 2007.
Jordan	2007	Marketing suspended. **Reference:** Communication from Jordan FDA, 3 April 2007.
Switzerland	June 2007	The Swiss Institute of Therapeutic Products, Swissmedic has declined to extend the marketing authorization for tegaserod (Zelmac) in Switzerland after a new analysis of clinical data showed that tegaserod had an increased risk of cardiovascular disorders compared with placebo. **References**: 1. Journal Swissmedic, p342, June 2007 (www.swissmedic.ch). 2. WHO Pharmaceuticals Newsletter No. 4, 2007.
USA	July 2007	The United States Food and Drug Administration (US FDA) has permitted the restricted use of tegaserod (Zelnorm) as an investigational new drug for the treatment of irritable bowel syndrome with constipation, and chronic idiopathic constipation. The use of tegaserod (Zelnorm) for such treatment is restricted to women aged < 55 years whose physicians decide that treatment with tegaserod is medically necessary. The US FDA had previously suspended the sales and marketing of tegaserod following a safety analysis that demonstrated an increased risk of myocardial infarction, stroke and unstable angina associated with tegaserod, compared with placebo. **References**: 1. FDA News. U.S. Food and Drug Administration, 27 July 2007 (www.fda.gov). 2. WHO Pharmaceuticals Newsletter No. 4, 2007.

Product Name: Telithromycin

CAS number: 173838-31-8

Other Names: Ketek

Country	Effective Date	Description of action taken Grounds for decision
Europe	March 2007	The EMEA has recommended restrictions on the use of telithromycin (Ketek) in three of its four approved indications: for the treatment of bronchitis, sinusitis

		and tonsillitis/pharyngitis; telithromycin should only be used for infections caused by bacterial strains that are suspected or proven to be resistant to or cannot be treated with macrolide or beta-lactam antibiotics. The Agency has recommended no restrictions for the remaining indication, the treatment of community-acquired pneumonia. The Agency has also recommended the contraindication of the use of telithromycin in patients with myasthenia gravis and strengthened warnings on transient loss of consciousness and effects on vision. These recommendations are based on the conclusions of a comprehensive review that the Agency has been carrying out since January 2006, following reports of severe liver injuries in patients taking telithromycin. **References**: 1. Press Release. EMEA, 30 March 2007 (www.emea.europa.eu). 2. WHO Pharmaceuticals Newsletter No. 2, 2007.
USA	February 2007	The US FDA has removed two of the three previously approved indications for telithromycin – acute bacterial sinusitis and acute bacterial exacerbations of chronic bronchitis. The Agency determined that the balance of benefits and risks no longer supported approval of telithromycin (Ketek) in the two indications. The antibacterial will remain on the market for the treatment of community-acquired pneumonia of mild-to-moderate severity. Additional changes include a boxed warning that telithromycin is contraindicated in patients with myasthenia gravis and a strengthened warning section regarding specific drug-related adverse events including visual disturbances and loss of consciousness. **References**: 1. Press Release. U.S. Food and Drug Administration, 12 February 2007 (www.fda.gov). 2. WHO Pharmaceuticals Newsletter No. 2, 2007.

Product Name: Terfenadine

CAS number: 50679-08-8

Other Names: 1-Piperidinebutanol; a-[4-(1,1-dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol

Country	Effective Date	Description of action taken Grounds for decision
Serbia	May 2005	Products containing terfenadine should not be used in patients who are concomitantly treated with CYP 3A4 inhibitors, proarrhythmic drugs, drugs that prolong QT interval, and with drugs that lead to electrolyte imbalance: serious cardiotoxic effects have been reported when terfenadine-containing products have

		been used in conjunction with these types of drugs. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, March 2005.

Product Name: Thioridazine

CAS number: 50-52-2

Other Names: Melleril

Country	Effective Date	Description of action taken Grounds for decision
Canada	30 September 2005	As of 30 September 2005, the sales of all thioridazine products have been discontinued in Canada, due to the lack of convincing benefit/harm information that support the continued safe use of the drug as an antipsychotic. Thioridazine will be available through the Special Access Programme in Canada for patients who cannot be adequately managed on alternative therapies. **Reference**: WHO Pharmaceuticals Newsletter No. 4, 2005.
Chile	9 June 2005	Indication restricted for use as second line treatment in schizophrenia that does not respond adequately to other antipsychotics. And the package inserts are required to include warnings of adverse cardiac events (e.g. QT prolongation) associated with the use of this medicine; contraindication in children below 18 years of age and in patients who are at risk for adverse cardiac events (history of arrhythmias etc). **Reference**: Resolución Nº 4689 de 9 de junio de 2005, la Dirección del Instituto de Salud Pública, Chile.
Democratic People's Republic of Korea	July 2005	Withdrawn due to safety concerns about QT-prolongation. **Reference:** Communication from Korea FDA, 6 April 2006.
Malaysia	June 2005	Following the voluntary cancellation of registration for Melleril^{R} by Novartis due to adverse cardiovascular events and poor benefit risk profile, a risk-benefit analysis of other generic products containing thioridazine was conducted. Based on this review, the Malaysian Regulatory Agency took the decision to disallow the continued use of thioridazine in Malaysia and the registration of these products was cancelled. **Reference**: Malaysian Adverse Drug Reactions Newsletter, Drug Control Authority, Ministry of Health, Malaysia, August 2005.

Turkey	July 2005	Suspended. **Reference:** Communication from the Turkish Pharmacovigilance Centre, 7 April 2006.
Ukraine	February 2005	Maximum daily dose limited to 300 mg/day. **Reference**: Information from the National Pharmacovigilance Centre, Ukraine, 2007.

Product Name: Tizanidine

CAS number: 51322-75-9

Other Names: 5-Chloro-N-(2-imidazolin-2-yl)-2,1,3-benzothiadiazol-4-ylamine hydrochloride

Country	Effective Date	Description of action taken Grounds for decision
Serbia	January 2006	Concomitant use of tizanidine with fluvoxamine or ciprofloxacin is contraindicated due to clinically significant interaction resulting in hypotension, somnolence, dizziness, decrease of psychomotor abilities. Concomitant use of tizanidine with antiarrhythmics (amiodarone, mexiletine, and propafenone), fluoroquinolones (enoxacin, perfloxacin and norfloxacin), oral contraceptives and ticlopidine is not recommended. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, December 2005.

Product Name: Trimethobenzamide

CAS number: 138-56-7

Other Names: Tigan; Tebamide

Country	Effective Date	Description of action taken Grounds for decision
USA	April 2007	The US FDA has announced that suppository products of trimethobenzamide are not approved to treat nausea and vomiting in adults or children because there is no evidence of their effectiveness. The Agency has asked the responsible companies to stop manufacturing and distributing these products which are marketed under various names (Tigan, Tebamide, T-Gen, Trimazide and Trimethobenz). This current action includes only the suppository forms and does not affect several oral capsules and injectable products containing trimethobenzamide that have been approved by the US FDA . Any company wishing to market a product containing

		trimethobenzamide in suppository form must now obtain an approved new drug application prior to marketing. **References**: 1. FDA News. U.S. Food and Drug Administration, 6 April 2007 (www.fda.gov). 2. WHO Pharmaceuticals Newsletter No. 3, 2007.

Product Name: Valdecoxib

CAS number: 181695-72-7

Other Names: Bextra

Country	Effective Date	Description of action taken Grounds for decision
Canada	April 2005	Sale suspended while awaiting evidence to establish the safety of this drug under the conditions of use for which it is recommended; and while awaiting risk benefit analysis from the manufacturer, indicating the unique therapeutic advantage **References**: 1. Advisory, Health Canada, 7 April 2005 (http://www.hc-sc.gc.ca). 2. WHO Pharmaceuticals Newsletter No. 3, 2005.
Chile	17 December 2004	Because of severe risk of adverse reactions, use not recommended in pain related to coronary bypass surgery. **Reference:** Communication from Chile Pharmacovigilance Centre, 2007.
Europe	March 2008	Having reviewed the Cox-2 inhibitors safety data, the EMEA issued a decision for suspension of the marketing authorization of valdecoxib in October 2005. **Reference**: Public Statement, EMEA, 27 March 2008 (www.emea.europa.eu).
Switzerland	2005	Provisional suspension (while awaiting additional information) due to reports of skin hypersensitivity reactions, myocardial infarction and cardiovascular risks. **Reference**: Information provided by Swissmedic, 2007.
USA	April 2005	The US FDA 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 NSAIDs. **Reference**: Public Health Advisory, U.S. Food and Drugs Administration, 7 April 2005 (www.fda.gov).

Product Name: Venlafaxine

CAS number: 93413-69-5

Other Names: Effexor

Country	Effective Date	Description of action taken Grounds for decision
UK	May 2006	The MHRA has introduced a smaller pack size to minimize the risk of overdose with the product. This is in addition to previous regulatory measures when concerns about potential cardiotoxicity and toxicity in overdose with venlafaxine led to the drug being restricted to specialist initiation and contraindicated in patients with heart disease. **References**: 1. Press Release. MHRA, 31 May 2006 (www.mhra.gov.uk). 2. WHO Pharmaceuticals Newsletter No. 4, 2006.

Product Name: Veralipride

CAS number: 66644-81-3

Other Names: Agreal

Country	Effective Date	Description of action taken Grounds for decision
Brazil	August 2007	Withdrawn with reference to EMEA's decision. **References**: 1. Alertas Federais de Farmacovigilância (www.anvisa.gov.br). 2. Communication from the Brazilian Pharmacovigilance Office, Brazilian Health Surveillance Agency (ANVISA), 5 September 2007.

Europe	Effective July 2007	The EMEA has recommended the withdrawal of the marketing authorization for medicinal products containing veralipride. The EMEA's Committee for Medicinal Products for Human Use (CHMP) concluded that the risks of veralipride (psychiatric and movement disorders) in the treatment of hot flushes associated with menopause in women are greater than its benefits and therefore recommended that the medicine should be taken off the market. **Reference**: Press Release. EMEA, 23 July 2007 (www.emea.europa.eu).

Product Name: Ximelagatran

CAS number: 192939-46-1

Other Names: Exanta

Country	Effective Date	Description of action taken Grounds for decision
Brazil	14 February 2006	Withdrawn due to evidence of hepatic risk. **Reference**: Communication from the Brazilian Pharmacovigilance Office, Brazilian Health Surveillance Agency (ANVISA), 5 September 2007 (www.anvisa.gov.br).
Switzerland	2006	Withdrawn due to hepatotoxicity. **Reference**: Information provided by Swissmedic, 2007.
UK	February 2006	Withdrawal of product from the market due to association with serious liver injury in patients in a trial (EXTEND trial) examining the use of the product in extended venous thromboembolism (VTE) prophylaxis in orthopaedic surgery. **Reference**: WHO Pharmaceuticals Newsletter No.2, 2006.

Product Name: Alimemazine - Paracetamol teething mixture

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
UK	February 2005	The MHRA issued a warning that a teething mixture containing alimemazine tartrate and paracetamol is contraindicated in children under the age of two years due to risk of adverse effects with the product in this population. **Reference**: WHO Pharmaceuticals Newsletter No. 2, 2005.

Product Name: Atazanavir-Ritonavir

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Europe	21 December 2004	Physicians have been warned against the co-administration of atazanavir (Reyataz) combined with ritonavir (RTV) and 40 mg omeprazole, or any other proton pump inhibitor based on the evidence that this type of co-administered statin could reduce the atazanavir exposure levels in these patients. **References**: 1. EMEA Public Statement,, 21 December 2004 (www.emea.eu.int). 2. WHO Pharmaceuticals Newsletter No. 1, 2005.

Product Name: Chlorproguanil and Dapsone

CAS number:

Other Names: LapDap

Country	Effective Date	Description of action taken Grounds for decision
Kenya	February 2008	GlaxoSmithKline has recalled LapDapTM, an anti-malarial product containing chlorproguanil and dapsone, based on the fact that significant reductions of haemoglobin levels have been observed in patients with glucose-6-phosphate dehydrogenase deficiency. **References**: 1. Press Release. GlaxoSmithKline and Medicines for Malaria Venture, 29 February 2008, London, UK;

		Geneva, Switzerland. 2. Review of the safety of chlorproguanil-dapson in the treatment of uncomplicated falciparum malaria in Africa: Report of a Technical Consultation convened by the World HealthOrganization. WHO, 2005, Switzerland. (ww.who.int/malaria/docs/LapDap.pdf). 3. Alert No. 117, Information Exchange System. WHO, 4 March 2008 (www.who.int/medicines).

Product Name: Cyproterone acetate and ethinylestradiol

CAS number:

Other Names: Diane-35

Country	Effective Date	Description of action taken Grounds for decision
Canada	May 2005	Health Canada has advised that ethinylestradiol/cyproterone (Diane-35) should not be used alone for contraception in women. These restrictions are based on evidence that women who used ethinylestradiol/cyproterone (Diane-35) appear to have a higher risk of blood clots than women who used combination oral contraceptives (Diane-35 is used in the treatment of acne). Health Canada advises that the product should be stopped 3–4 months after the complete resolution of the signs of acne. **Reference**: WHO Pharmaceuticals Newsletter No. 3, 2005.

Product Name: Dextropropoxyphene-paracetamol

CAS number

Other Names: Capadex, Paradex

Country	Effective Date	Description of action taken Grounds for decision
New Zealand	2006	The following restrictions in use have been recommended for this combination product, following reports of deaths associated with intentional and accidental overdose: • narrowing of the indication to the relief of chronic pain of moderate severity; • restriction to second-line therapy for patients who have not tolerated, or have inadequately responded to therapeutic doses of alternative analgesics; • restriction of the recommended dose to two tablets up to every four hours, with a maximum daily dose of eight tablets (equivalent to paracetamol 2.6 g);

		• reducing the dose in the elderly and in patients with renal or hepatic impairment. Prescribers are advised to avoid the concurrent use of these products with alcohol or with other paracetamol-containing products, and to warrant caution while prescribing them in patients receiving anxiolytics or antidepressants. **References**: 1. Prescriber Update, Vol. 27(2): 21, 2006 (www.medsafe.gov.nz). 2. WHO Pharmaceuticals Newsletter No. 6, 2006.

Product Name: Estradiol-testosterone injection

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Canada	2005	Discontinued as a hormone replacement therapy due to potential adverse effects such as endometrial hyperplasia or carcinoma, hirsuitism, aggression and virilisation in women. **References**: 1. Advisories, Warnings and Recalls. Health Canada, 23 November 2005 (www.hc-sc.gc.ca). 2. WHO Pharmaceuticals Newsletter No. 1, 2006.

Product Name: Ingalipt (Combination aerosol)

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Armenia	2005	Scientific Centre of Drug and Medical Technology Expertise Ministry of Health (SCDMTE MoH) did not approve the marketing of Ingalipt (complex for local treatment of inflammation/infection of oral-throat localization) because combination of two sulfonamides in one medicine was estimated as irrational. **Reference** Communication from the Armenian Drug Regulatory Authority, 2007.

Product Name: Metamizole, pitofenone and fenpiverinium

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Serbia	May 2005	The labels are required to include the boxed warning: "The use is not recommended in children and adolescents under the age of 18 years." The use has been restricted to short-term treatment of severe pains caused by smooth muscles' spasm where other therapy shows ineffectiveness. These measures refer to all registered combination products containing metamizole and a spasmolytic drug. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, March 2005.

Product Name: Triaminic vapour patch

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Canada	May 2006	Health Canada issued a warning that it is recalling Triaminic Vapour Patch, a product that contains camphor, eucalyptus oil and menthol, because of a risk of ingestion by children with serious adverse outcome. **Reference**: Advisories, Warnings and Recalls. Health Canada, 30 May 2006 (www.hc-sc.gc.ca).
USA	June 2006	A nationwide voluntary recall of all Triaminic Vapor Patch products has been conducted in the USA by Novartis Consumer Health. **Reference**: Public Health Advisory. U.S. Food and Drug Administration, 20 June 2006 (www.fda.gov).

Product Name: Angiotension Converting Enzyme (ACE) inhibitors and Angiotensin II receptor antagonists

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Malaysia	October 2006	The following statement must be included on labels and package inserts of all products containing ACE Inhibitors including the combination under the “Warning" and “Use for Pregnancy” sections:- • “Increased risk of birth defects, foetal and neonatal morbidity and death when used throughout pregnancy”. **Reference**: Communication from the Malaysian National Pharmacovigilance Centre, 2007.
UK	December 2007	The MHRA has advised that ACE inhibitors and angiotensin II receptor antagonists should not be used at any stage of pregnancy due to the risk of congenital anomalies. **References**: 1. Drug Safety Update Vol. 1 (5): 9, December 2007 (www.mhra.gov.uk). 2. WHO Pharmaceuticals Newsletter No.1, 2008.

Product Name: Attention-Deficit/Hyperactivity Disorder (ADHD) drugs

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Canada	May 2006	Health professionals have been advised that ADHD drugs should be started at the lowest dose and increased slowly, and should not be given to patients with a symptomatic heart disorder, advanced arteriosclerosis, hyperthyroidism, moderate to severe hypertension, or structural cardiac abnormalities; further cardiovascular (CV) system evaluation may be considered before starting ADHD drugs in patients with relevant risk factors, and patients who require long-term ADHD drugs should undergo periodic CV status evaluation. This applies to the following drugs and all products containing these drugs: methylphenidate (e.g. Ritalin) and methylphenidate extended release (Ritalin SR), dexmethylphenidate (Attenade), dexamfetamine (Dexedrine), atomoxetine (Strattera). **References**: 1. Advisories, Warnings and Recalls, Health Canada,

		26 May 2006 (www.hc-sc.gc.ca). 2. WHO Pharmaceuticals Newsletter No. 4, 2006.

Product Name: Alendronic acid and other bisphosphonates

CAS number: 66376-36-1

Other Names: 4-Amino-1-hydroxybutane-1, 1-diylbis(phosphonic acid); Aminohydroxybutylidene Diphosphonic Acid

Country	Effective Date	Description of action taken Grounds for decision
Serbia	December 2006	Due to risk of jaw osteonecrosis, precaution is required, especially in cancer patients treated with corticosteroids and chemotherapy, as well as in patients with tooth extraction or local infection. Dental examination and preventive measures before including bisphosphonates in therapy are recommended in patients with additional risk factors. This measure refers to all registered oral and parenteral products containing bisphosphonates, including generic alendronate. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, October 2006.

Product Name: Antidepressants

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Chile	5 January 2005	Heath-care professionals and patients have been informed that suicidal thoughts and aggressive behaviour have been observed in children receiving antidepressant treatment for major depression, obsessive compulsive disorder or other mood disorders. The labels for these products are required to note the above adverse events and that this population needs to be monitored closely during antidepressant treatment for signs of suicidal thoughts and that they may not be used in children below the age of 18 years. **Reference**: Resolución Nº 380 de 5 de enero de 2005, la Dirección del Instituto de Salud Pública, Chile.
Serbia	August 2005	Special warning has been issued concerning suicidal behaviours and aggression in children and adolescents under the age of 18 years using antidepressives. This measure refers to all registered original and generic products containing selective serotonin

		reuptake inhibitors (SSRI) (paroxetine, citalopram, sertraline, escitalopram) and some other antidepressants (mianserin, mirtazapine, venlafaxine). **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, June 2005.

Product Name: Antiretroviral agents

Caution advised against certain combinations

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Canada		To avoid virologic failure and emergence of resistance, the co-administration of didanosine and tenofovir should be undertaken with caution; patients who are receiving both drugs should be monitored carefully for continued efficacy and for adverse events (AEs); and didanosine should be discontinued in patients who develop AEs associated with the drug. **Reference**: 'Dear Health-care Professional' letter from Bristol Myers Squibb and Gilead Sciences, Canada, 9 June 2005 (www.hc-sc.gc,ca).

Product Name: Betamethasone and other potent corticosteroids for topical use

CAS number:

Other Names: 9α-Fluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione; 9α-Fluoro-16β-methylprednisolone

Country	Effective Date	Description of action taken Grounds for decision
Serbia	July 2007	Not indicated in children under the age of one year, and should not be used for longer than seven days without physician's monitoring. Contraindicated in treatment of acne rosacea, perioral dermatitis, perianal/genital pruritus, plaque psoriasis and tuberculosis of skin, primary bacterial and virus skin infections, mycosis, as well as in hypersensitive patients. Children's growth and development can be affected by chronic use of corticosteroid; therefore precaution is required for use in children under the age of two years. Administration on face is not recommended; if it is needed, careful use for up to five days is required. In case of irritation or hypersensitivity reactions, discontinuation of therapy is required. These measures refer to all registered topical

		products containing potent corticosteroids (betamethasone, fluocinolone acetonide, diflucortolone, and desoximethasone). **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, June 2007.

Product Name: Black Cohosh *(Cimicifugae racemosae)*-containing products

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Malaysia	July 2006	All Black Cohosh containing products should carry the following precautionary statement: • Stop taking this product if signs and symptoms suggestive of liver injury develop such as tiredness, loss of appetite, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine, and consult your doctor immediately. • Patients using herbal medicinal products should tell their doctor about it. **Reference**: Communication from the Malaysian National Pharmacovigilance Centre, 2007.

Product Name: Chelidonium extract

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Switzerland	2007	Extracts containing more than 0.3 mg product of total alkaloid have been withdrawn due to hepatotoxicity with a total daily alkaloid ingestion > 0.3 mg. **Reference**: Communication from Swissmedic, 2007.

Product Name: Clobutinol-containing cough preparations

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Europe	October 2007	The EMEA has recommended withdrawing the marketing authorization for cough medicines containing clobutinol. This recommendation is based on the Agency's review of the safety of clobutinol and

		its conclusion that the use of clobutinol is linked to a clear risk of QT prolongation, the benefits of medicines containing clobutinol therefore no longer outweigh their risks. Boehringer Ingelheim laboratories (manufacturer of clobutinol-containing products) have announced their decision to voluntarily withdraw the product (Silomat) from the global markets. **References**: 1. Press Release, EMEA, 18 October 2007 (www.emea.europa.eu). 2. WHO Pharmaceuticals Newsletter No. 5, 2007.

Product Name: Cyclo-oxygenase-2 (COX-2) Inhibitors

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Chile	8 June 2005	The package insert for this class of drugs is required to indicate that these products are contraindicated in patients with ischaemic heart disease (present or past) or cardiac insuffiiciency; that they should not be used in the immediate postoperative period following by-pass surgery; and to use with caution in patients with cardiovascular risks such as hypertension, hyperlipidemia, diabetes etc. These measures have been recommended because of adverse cardiovascular events that have been reported with COX-2 inhibitors. **Reference:** Resolución Nº 4575 de 8 de junio de 2005, la Dirección del Instituto de Salud Pública, Chile.
New Zealand	February 2005	COX-2 inhibitors will be available only under very strict restrictions in the New Zealand market. These products should be contraindicated in patients with previous MI or stroke and perioperatively for cardiac or vascular surgery, and perioperatively for major surgery in patients at high cardiovascular (CV) risk; COX-2 inhibitors should not be used if alternatives exist, and, if used, the lowest effective dose should be used for the shortest possible duration; patients should be reviewed after two weeks, with treatment discontinued if there is no benefit, then reviewed every three months. This decision was based on the recommendations of Medicine Adverse Reaction Committee (MARC)on the benefits and risks of COX-2 inhibitors. **References**: 1. Media Release. Medsafe, 29 April 2005 (ww.medsafe.govt.nz). 2. Alert / letter to doctors and pharmacists,

		Medsafe, 29 April 2005 (www.medsafe.govt.nz). 3. WHO Pharmaceuticals Newsletter No. 3, 2005.
Malaysia	June 2005	The following statement has been included in the package inserts of products containing COX-2 Inhibitors: • COX-2 inhibitors be used as second line therapy. • Contraindicated in patients with the risk of ischaemic heart disease and stroke. • Prescribed with care in patients predisposed to the risk of hypertension, hyperlipidaemia, heart disease, peripheral arterial disease and in smokers. • The lowest effective dose for the shortest possible duration should be used. **Reference**: Communication from the Drug Regulatory Authority, Ministry of Health, Malaysia.

Product Name: Drug-eluting stents

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Sweden	February 2007	The Swedish Medical Products Agency (MPA), in conjunction with the National Board of Health and Welfare and the Swedish Society of Cardiology, has recommended utmost restraint in the use of drug-eluting stents. The recommendation was based on the results of clinical studies, including the Swedish Coronary and Angioplasty Registry (SCAAR) study that showed increased risk of thrombosis associated with the use of drug-eluting stents. According to the MPA, drug-eluting stents must only be used in patients for whom no other treatment alternative exists or in patients who are at greatly increased risk of restenosis and for whom the effect of restenosis is expected to be severe. **References**: 1. WHO Pharmaceuticals Newsletter No. 2, 2007. 2. Swedish Medical Products Agency communication, 13 February 2007 (www.lakemedelesverket.se).

Product Name: Ephedrine and pseudoephedrine containing OTC products

CAS number:

Other Names:

Country	Effective	Description of action taken

	Date	Grounds for decision
UK	October 2007	OTC nasal decongestant products that contain pseudoephedrine and ephedrine are to be placed under tighter control in the UK due to the increasing concern that pseudoephedrine and ephedrine in these products can be extracted and used in the illegal manufacture of methylamfetamine (crystal meth). Large packs of pseudoephedrine and ephedrine are to be replaced by smaller packs of 720 mg (the equivalent of 12 tablets or capsules of 60 mg or 24 tablets or capsules of 30 mg) and a sale limit of one pack per customer will apply. **References**: 1. Press Release, MHRA, 29 August 2007 (www.mhra.gov.uk). 2. WHO Pharmaceuticals Newsletter No. 5, 2007.

Product Name: Nasal/oropharyngeal antibiotics

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
France	30 September 2005	The French medicines regulatory agency (AFSSAPS), has ordered that preparations of the antibiotics bacitracin, fusafungine, gramicidin or tyrothricin, which are locally administered (nasally or by oropharynx route) should be withdrawn from the market due to a lack of therapeutic efficacy. The Agency is of the opinion that such a move would also prevent the emergence of strains of antibiotic-resistant bacteria. These measures are consistent with AFSSAPS' recently completed review of locally administered antibiotics as part of a national and European action programme to promote the proper use of antibiotics. **Reference**: Letter to prescribers, AFSSAPS, 19 July 2005 (recherche.sante.gouv.fr).

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

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Chile	9 June 2005	Product insert to indicate that these agents are contraindicated in patients who are hypersensitive to one of the other NSAIDs, patients suffering from asthma, rhinitis, urticaria, angioedema,

		bronchospasm, and anaphylactic reactions to acetyl salicylic acid preparations. The warning section should refer to adverse gastrointestinal effects, potential for adverse cardiac and hepatic effects with nimesulide, sulindac, diclofenac and naproxen; and to use NSAID with caution in patients with renal problems. **Reference:** Resolución Nº 4687 de 9 de junio de 2005, la Dirección del Instituto, de Salud Pública, Chile.

Product Name: Products containing Ginseng

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Malaysia	June 2005	Labelling requirement for traditional medicines containing ginseng has been changed from "Continuous use exceeding three months not advisable" to "Safety on long-term use has not been established". **Reference**: Communication from the Drug Regulatory Authority, Ministry of Health, Malaysia.

Product Name: Propolis and Royal Jelly Products

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Malaysia	July 2005	Royal Jelly For traditional medicines containing Royal Jelly, the product label must carry the following statements: • Royal jelly may cause severe allergic reactions including fatal anaphylactic reactions in susceptible individuals. • Asthma and allergy sufferers may be at a greater risk. This is due to the fact that Royal Jelly has been identified as a possible cause of contact dermatitis, bronchospasm, anaphylaxis, asthma, urticaria and rhinitis. Propolis For traditional medicines for topical use containing Propolis, the product label must carry the following statement: • Propolis may cause allergic skin reactions. **Reference**:

		Communication from the Drug Regulatory Authority, Ministry of Health, Malaysia.

Product Name: Risperidone and other atypical antipsychotics

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
Serbia	April 2006	Additional warning has been issued against the use of these products in elderly patients with dementia due to high incidence of cerebrovascular adverse reactions. This measure refers to all registered original and generic products containing risperidone and to other registered atypical antipsychotics (olanzapine and ziprasidone). Precaution required for the combined use of risperidone and furosemide due to interaction of unknown mechanism leading to increased mortality. For use of products containing risperidone or olanzapine, monitoring of patients is recommended due to risk of hyperglycaemia or diabetes exacerbation. **Reference**: Communication from the National Pharmacovigilance Centre of Serbia, December 2005.

Product Name: Thiazolidinedione antidiabetics

CAS number:

Other Names:

Country	Effective Date	Description of action taken Grounds for decision
USA		The US FDA, based on a review of postmarketing adverse events reports, has requested the addition of a boxed warning on the label about the risk of heart failure for all thiazolidinedione class of antidiabetic drugs. This class includes rosiglitazone (Avandia), pioglitazone (Actos), rosiglitazone and glimepiride (Avandaryl), among others. The warning also states that these drugs should not be used by people with serious or severe heart failure. US FDA's review of the postmarketing adverse events reports found cases of significant weight gain, and oedema, both of which are warning signs of heart failure; some reports were associated with poor treatment outcomes, including death, when treatment was continued. **Reference**: FDA News. U.S. Food and Drug Administration, 14 August 2007 (www.fda.gov).