

Appendix 1 (as supplied by the author): Supplementary tables

Supplementary Table A1: New Active Substances approved 1990-1994

Generic name	Brand name	Date of Notice of Compliance (market approval)	Anatomical Therapeutic Chemical 2nd level	Dates of safety warnings	Reason for safety warning	Days from NOC to first safety warning	Date of withdrawal	Reason for withdrawal	Days from NOC to withdrawal	Biologic (B) or Small Molecule (SM)
SELEGILINE	ELDEPRYL	02/01/1990	anti-parkinson drugs			10335				SM
FLUNARIZINE	SIBELIUM	10/01/1990	other nervous system drugs			10327				SM
RECOMBINANT HUMAN ERYTHROPOIETIN	EPREX	16/02/1990	antianemic preparations	2001-11-26; 2002-06-25; 2004-01-13; 2004-10-13; 2007-04-16	pure red cell aplasia; pure red cell aplasia; subcutaneous use may increase risk of immunogenicity; thrombotic vascular events; increased risk of death if hemoglobin targeted >120	4301				B
CEFOTETAN	CEFOTAN	08/03/1990	antibacterials for systemic use			10270				SM
CEFOTETAN	CEFOTAN	08/03/1990	antibacterials for systemic use			10270				SM
BOTULINUM TOXIN TYPE A	OCULINUM	14/03/1990	muscle relaxants			10264				B
FENOFIBRATE	LIPIDIL	20/04/1990	lipid modifying agents	07/11/2012	if already taking more than 10 mg of simvastatin risk of myopathy/rhabdomyolysis	8237				SM
Bacillus Calmette-Guerin	BCG THERAPEUTIC	25/04/1990	immunostimulants			10222				B
KETOTIFEN	ZADITEN	04/05/1990	antihistamines for systemic use	01/10/2000	sleep apnea	3803				SM
LEVAMISOLE	ERGAMISOL	04/05/1990	anthelmintics				17/10/2003	agranulocytosis	4914	SM
NEDOCROMIL	TILADE	13/06/1990	drugs for obstructive airway diseases			10173				SM
PROPOFOL	DIPRIVAN	15/06/1990	anesthetics	1995-10-01; 2001-02-13; 2001-05-01; 2017-12-22	convulsions; metabolic acidosis, rhabdomyolysis, cardiac failure with use more than 48 hours; not recommended in children under 18; development of children's brains	1934				SM
TIXOCORTOL	RECTOVALONE	15/06/1990	antidiarrheals, intestinal antiinflammatory/antiinfective agents			10171				SM
FLUVOXAMINE	LUVOX	05/07/1990	psychoanaleptics	1996-01-01; 1998-10-01; 2000-07-31; 2003-01-30; 2004-05-01; 2004-06-03; 2004-08-09; 2006-03-10	hyponatremia; don't use with thioridazine; discontinuation reaction; don't use with ergotamine and dihydroergotamine containing drugs; increased risk of self-harm; increased risk of self-harm; harm to newborns if mother taking; serious lung disorder in newborn	2006				SM
ZOPICLONE	IMOVANE	02/08/1990	psycholeptics	2009-10-07; 2014-11-19	complex sleep-related behaviours; dosage reduction to reduce next-day impairment	7006				SM
FLUCONAZOLE	DIFLUCAN	27/08/1990	antimycotics for systemic use	1997-01-01; 2003-01-30; 2005-09-13	congenital anomalies; don't use with ergotamine and dihydroergotamine containing drugs; may cause hypoventilation if used with fentanyl transdermal system	2319				SM
NICARDIPINE	CARDENE	29/08/1990	calcium channel blockers	23/01/1996	increased risk of myocardial infarction	1973				SM
PRAVASTATIN	PRAVACHOL	29/08/1990	lipid modifying agents	1994-03-01; 2005-07-12; 2013-01-24	rhabdomyolysis; increased risk of diabetes	1280				SM
SIMVASTATIN	ZOCOR	29/08/1990	lipid modifying agents	1994-03-01; 2005-07-12; 2012-11-07 2013-01-24	shabdomyolysis; rhabdomyolysis; increased risk of diabetes	1280				SM

TERCONAZOLE	TERAZOL 7	20/09/1990	gynecological antiinfectives and antiseptics	1997-10-01; 2014-06-09	erythema multiforme; anaphylaxis and toxic epidermal necrolysis	2568		SM
OLSALAZINE	DIPENTUM	11/10/1990	antidiarrheals, intestinal antiinflammatory/antiinfec tive agents			10053		SM
ZIDOVUDINE	RETROVIR	17/10/1990	antivirals for systemic use			10047		SM
MOMETASONE	ELOCOM	22/10/1990	corticosteroids, dermatological preparations			10042		SM
LISINAPRIL	PRINIVIL	26/10/1990	agents acting on the renin-angiotensin system	1993-08-01; 1997-07-01; 2006-06-29; 2014-02-04	chronic renal failure; bronchospasm; increased risk of birth defects; don't combine with aliskiren or ARBs	1010		SM
LISINAPRIL	ZESTRIL	26/10/1990	agents acting on the renin-angiotensin system	1993-08-01; 1997-07-01; 2006-06-29; 2014-02-04	chronic renal failure; bronchospasm; increased risk of birth defects; don't combine with aliskiren or ARBs	1010		SM
IOVERSOL	OPTIRAY	01/11/1990	contrast media	24/04/2017	hypothyroidism	9671		SM
KETOROLAC	TORADOL	14/11/1990	antiinflammatory and antirheumatic products	1992-05-01; 1992-11-27; 2000-10-01	gastrointestinal bleeding; gastrointestinal bleeding, allergic reaction; corneal ulceration	534		SM
ANISTREPLASE	EMINASE	18/03/1991	antithrombotic agents			9895		B
MAFARELIN	Oculinum	18/03/1991	pituitary and hypothalamic hormones and analogues			9895		SM
CLOZAPINE	CLOZARIL	20/03/1991	psycholeptics	2002-01-14; 2004-06-23; 2005-06-15; 2005-06-30; 2011-06-15	cardiovascular toxicity; changes in Product Monograph; increased mortality in patients with dementia; white blood cell monitoring; abnormal muscle movements and withdrawal symptoms in newborns	3953		SM
ASIATICOSIDE, MADECASSOID	COTHILYNE	26/03/1991	preparations for treatment of wounds and ulcers			9887		SM
IDARUBICIN	IDAMYCIN	03/04/1991	antineoplastic agents			9879		SM
TICLOPIDINE	TICLID	22/04/1991	antithrombotic agents	1993-11-01; 1995-07-01; 1999-10-01	hematological & liver disorders; irreversible neutropenia; serious hematological reaction	924		SM
ONDANESTRON	ZOFRAN	06/05/1991	antiemetics and antinauseants	2012-10-03; 2014-05-14; 2014-06-12	dose dependent QT prolongation; potential risk of serotonin syndrome; risk of QT prolongation in elderly patients	7821		SM
CETIRIZINE	REACTINE	28/05/1991	antihistamines for systemic use			9824		SM
AZTREONAM	AZACTAM	29/05/1991	antibacterials for systemic use			9823		SM
LODOXAMIDE	ALOMIDE	27/06/1991	ophthalmologicals			9794		SM
MIDODRINE	AMATINE	27/06/1991	cardiac therapy			9794		SM
PERGOLIDE	PERMAX	27/06/1991	anti-parkinson drugs	2003-04-17; 2004-01-01 2004-10-12	valvulopathy; sudden onset of sleep; valvulopathy or fibrosis	4312	30/08/2007 valvulopathy	5908 SM
TENOXCAM	MOBIFLEX	27/06/1991	antiinflammatory and antirheumatic products			9794		SM
COLFOSCERIL	EXOSURF NEONATEL	28/06/1991	other respiratory system products			9793		SM
OFLOXACIN	FLOXIN	28/06/1991	antibacterials for systemic use	2011-11-07; 2017-01-23	increased muscle weakness in patients with myasthenia; tendinopathy, peripheral neuropathy & CNS disorders	7437		SM
FLUMAZENIL	ANEXATE	30/08/1991	all other therapeutic products			9730		SM
HAEMOPHILUS B CONJUGATE VACCINE	HIBTITER	30/08/1991	vaccines			9730		B

HAEMOPHILUS B CONJUGATE-MENIN GITIS VACCINE	PEDVAXHIB	31/08/1991	vaccines			9729	B
URSODIOL	URSOFALK	13/09/1991	bile and liver therapy	01/12/2011	serious hepatic adverse events	7384	SM
DIGOXIN IMMUNE FAB	DIGIBIND	26/09/1991	all other therapeutic products			9703	B
DOXAZOSIN	CARDURA	30/09/1991	antihypertensives			9699	SM
DIDANOSINE	VIDEX BUFFERED POWDER	08/10/1991	antivirals for systemic use	2001-01-01; 2001-03-28; 2004-03-08; 2005-06-09	fatal lactic acidosis when used with stavudine; hepatotoxicity and pancreatitis with hydroxyurea; use with caution with tenofovir; use didanosine + tenofovir with caution with either efavirenz or nevirapine	3373	SM
DIDANOSINE	VIDEX CHEWABLE	08/10/1991	antivirals for systemic use	2001-01-01; 2001-03-28; 2004-03-08; 2005-06-09	fatal lactic acidosis when used with stavudine; hepatotoxicity and pancreatitis with hydroxyurea; use with caution with tenofovir; use didanosine + tenofovir with caution with either efavirenz or nevirapine	3373	SM
DIDANOSINE	VIDEX PEDIATRIC POWDER	08/10/1991	antivirals for systemic use	2001-01-01; 2001-03-28; 2004-03-08; 2005-06-09	fatal lactic acidosis when used with stavudine; hepatotoxicity and pancreatitis with hydroxyurea; use with caution with tenofovir; use didanosine + tenofovir with caution with either efavirenz or nevirapine	3373	SM
ENOXACIN	COMPRECIN	23/10/1991	antibacterials for systemic use	01/04/1995	joint pain and achilles tendonitis	1256	SM
PODOPHYLLOTOXIN	CONDYLINE	23/10/1991	antibiotics and chemotherapeutics for dermatological use			9626	SM
SULBACTAM + AMPICILLIN	UNASYN	12/12/1991	antibacterials for systemic use			9626	SM
NILUTAMIDE	ANANDRON	20/12/1991	endocrine therapy			9618	SM
FELODIPINE	PLENDIL	24/12/1991	calcium channel blockers	23/01/1996	increased risk of myocardial infarction	1491	SM
QUINAPRIL	ACCUPRIL	14/01/1992	agents acting on the renin-angiotensin system	1997-07-01; 2006-06-29; 2014-02-04	increased risk of birth defects; bronchospasm; don't combine with aliskiren or ARBs	1995	SM
SUMATRIPTAN	IMITREX	20/01/1992	analgesics	1993-08-01; 1995-01-01	coronary vasospasm, respiratory disorder; rebound headache and migraine exacerbation	559	SM
ESMOLOL	BREVIBLOC	24/01/1992	beta blocking agents			9583	SM
SERTRALINE	ZOLOFT	30/01/1992	psychoanalitics	1998-10-01; 1999-01-01; 2003-02-28; 2004-06-03; 2004-08-09; 2006-03-10	don't use with pimozide; interaction with carbamazepine; discontinuation reaction; increased risk of self-harm; harm to newborn if mother taking; serious lung disorder in newborn	2436	SM
FILGRASTIM	NEUPOGEN	11/02/1992	immunostimulants	10/04/2014	capillary leak syndrome	8094	B
CEFONICID	MONOCID	17/02/1992	antibacterials for systemic use			9559	SM
BUMETANIDE	BURINEX	26/02/1992	diuretics			9550	SM
PAMIDRONATE	AREDIA	26/02/1992	drugs for treatment of bone diseases	05/11/2004	osteonecrosis of jaw	4636	SM
PENTASTARCH	PENTASPAN	27/02/1992	blood substitutes and perfusion solutions	18/07/2013	increased mortality and severe renal injury	7812	SM
CIPROFLOXACIN	CILOXAN	17/03/1992	ophthalmologicals			9530	SM
DAPIPRAZOLE	REV EYES	17/03/1992	ophthalmologicals			9530	SM

HAEMOPHILUS B CONJUGATE VACCINE/ TETANUS PROTEIN-CONJUGATE	ACT-HIB	19/03/1992	vaccines			9528	B
APRACLONIDINE	IOPIDINE	25/03/1992	ophthalmologicals			9522	SM
FOSINOPRIL	MONOPRIL	09/04/1992	agents acting on the renin-angiotensin system	1993-08-01; 1997-07-01; 2006-06-29; 2014-02-04	chronic renal failure; bronchospasm; increased risk of birth defects; don't combine with aliskiren or ARBs	479	SM
DOXACURIUM	NUROMAX	15/04/1992	muscle relaxants			9501	SM
CLOSTRIDIUM BOTULINUM TOXIN TYPE A	BOTOX	05/05/1992	other drugs for disorders of the musculo-skeletal system	2008-02-20; 2008-12-22	distant spread of toxin; muscle weakness remote to site of injection	5769	B
CLARITHROMYCIN	BIAXIN	08/05/1992	antibacterials for systemic use	1996-07-01; 2003-01-30	tooth discolouration, smell alteration; don't use with ergotamine and dihydroergotamine containing drugs	1515	SM
CLODRONATE	BONEFOS	11/05/1992	drugs for treatment of bone diseases			9475	SM
GALLIUM	GANITE	02/06/1992	diagnostic radiopharmaceuticals			9453	SM
FLUDARABINE	FLUDARA	16/06/1992	antineoplastic agents	2004-07-24; 2008-11-18	possible reactivation of hepatitis B; infection-related death if used with rituximab	4421	SM
GADOPENTETATE	MAGNEVIST	22/06/1992	contrast media	2007-03-09; 2013-11-14; 2017-01-05	nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy; nephrogenic systemic fibrosis; may accumulate in brain	5373	SM
AMLODIPINE	NORVASC	26/06/1992	calcium channel blockers	1996-01-23; 1999-07-01; 2012-11-07	increased risk of myocardial infarction; hearing loss; limit dose of simvastatin when used with amlodipine	1306	SM
ZALCITABINE	HIVID	07/07/1992	antivirals for systemic use			9418	SM
DIPHTHERIA AND TETANUS TOXOIDS ADSORBED, PERTUSSIS VACCINE COMBINED WITH HAEMOPHILUS B, CONJUGATE VACCINE	DPT-HIB	29/07/1992	vaccines			9396	SM
HUMAN GONADOTROPIN	HUMEGON	31/07/1992	sex hormones and modulators of the genital system	01/10/1995	ovarian hyperstimulation	1157	B
MOCLOBEMIDE	MANERIX	12/08/1992	psychoanaleptics			9382	SM
TYPHOID VACCINE LIVE	VIVOTIF BERNA	21/08/1992	vaccines			9373	B
MILRINONE	PRIMACOR	10/09/1992	cardiac therapy			9353	SM
EDOXUDINE	VIROSTAT	22/09/1992	antibiotics and chemotherapeutics for dermatological use			9341	SM
ADENOSINE	ADENOSCAN	19/10/1992	cardiac therapy			9314	SM
FINASTERIDE	PROSCAR	23/10/1992	urologicals	2011-08-04; 2012-03-19	rare risk of breast cancer in men; may increase risk of high-grade prostate cancer	6859	SM
CALCIPOTRIOL	DOVONEX	27/10/1992	antipsoriatics			9306	SM
LOMEFLOXACIN	MAXAQUIN	27/10/1992	antibacterials for systemic use			9306	SM
PENTOSTATIN	NIPENT	06/11/1992	antineoplastic agents			9296	SM
MECLOFENAMIC ACID	MECLOMEN	20/11/1992	antiinflammatory and antirheumatic products			9282	SM
ATOVAQUONE	MEPRON	25/11/1992	antiprotozoals			9277	SM
RECOMBINANT ANTIHEMOPHILIC FACTOR	RECOMBINATE	10/12/1992	antihemorrhagics			9262	B
NAFTIFINE	NAFTIN	21/12/1992	antifungals for dermatological use			9251	SM

GADOTERIDOL	PROHANCE	23/12/1992	contrast media	2007-03-09; 2013-11-14; 2017-01-05	nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy; may accumulate in brain	5189	SM
ESTAZOLAM	PROSOM	29/12/1992	psycholeptics			9243	SM
PACLITAXEL	TAXOL	29/12/1992	antineoplastic agents			9243	SM
HALOBETASOL	ULTRAVATE	22/01/1993	corticosteroids, dermatological preparations			9219	SM
MEFLOQUINE	LARIAM	22/01/1993	antiprotozoals	1998-01-01; 2005-01-01	QT prolongation, neuropsychiatric reactions; mental and heart problems	1805	SM
BERACTANT	SURVANTA	29/01/1993	other respiratory system products			9212	B
ENOXAPARIN	LOVENOX	09/02/1993	antithrombotic agents			9201	SM
LEVOCABASTINE	LIVOSTIN	09/02/1993	nasal preparations			9201	SM
ISRADIPINE	DYNACIRC	16/02/1993	calcium channel blockers			9194	SM
CLADRIBINE	LEUSTATIN	18/03/1993	antineoplastic agents			9164	SM
CILAZAPRIL	INHIBACE	22/03/1993	agents acting on the renin-angiotensin system	1997-07-01; 2006-06-29; 2014-02-04	increased risk of birth defects; bronchospasm; don't combine with aliskiren or ARBs	1562	SM
RIFABUTIN	MYCOBUTIN	23/03/1993	antimycobacterials			9159	SM
RHO(D) IMMUNE GLOBULIN	WINRHO	01/04/1993	immune sera and immunoglobulins	2000-10-01; 2006-01-24; 2010-03-22	hemolytic and renal adverse reactions; intravascular hemolysis; don't use in patients with ITP	2740	B
PORFIMER	PHOTOFRIN	19/04/1993	antineoplastic agents			9132	B
RISPERIDONE	RISPERDAL	23/04/1993	psycholeptics	1995-01-01; 1998-04-01; 2002-10-11; 2002-10-17; 2005-06-15; 2008-07-15; 2011-06-15; 2013-11-14; 2015-02-18	extra-pyramidal symptoms; increase in carbamazepine level; cerebrovascular adverse events; stroke and stroke- like events; increased mortality in patients with dementia; increased water retention and hyponatremia if used with DDAVP; abnormal muscle movements and withdrawal symptoms in newborns; intraoperative floppy iris syndrome; restricted indication for use in patients with dementia	618	SM
PENTOSAN	ELMIRON	26/04/1993	vasoprotectives			9125	SM
PAROXETINE	PAXIL	04/05/1993	psychoanaleptics	1996-01-01; 1998-10-01; 2000-07-31; 2003-07-10 2004-06-03; 2004-08-09; 2005-09-29; 2005;12-16; 2006-03-10	hyponatremia; discontinuation reaction; don't use with thioridazine; don't use in pediatric patients; increased risk of self-harm; harm to newborn if mother taking; increased risk of congenital malformations; risk of cardiac defects in newborn; serious lung disorder in newborn	972	SM
TERBINAFINE	LAMISIL	04/05/1993	antifungals for dermatological use	1994-07-01; 1996-01-01; 2001-05-17	hematological disorders; hepatobiliary reactions; don't use in patients with liver damage	423	SM
BENAZEPRIL	LOTENSIN	14/06/1993	agents acting on the renin-angiotensin system	1993-08-01; 1997-07-01; 2006-06-29; 2014-02-04	chronic renal failure; bronchospasm; increased risk of birth defects; don't combine with aliskiren or ARBs	48	SM
DESOGESTREL/ETHI NYL ESTRADIOL	MARVELON	13/07/1993	sex hormones and modulators of the genital system			9047	SM

DESOGESTREL/ETHINYL ESTRADIOL	ORTHO-CEPT	13/07/1993	sex hormones and modulators of the genital system			9047	SM
LORACARBEF	LORABID	19/07/1993	antibacterials for systemic use			9041	SM
SALSALATE	DISALCID	19/07/1993	analgesics			9041	SM
REMOXIPRIDE	ROXIAM	26/07/1993	psycholeptics			14/03/1994	aplastic anemia 231
IOPENTOL	RHEOPAQUE	09/08/1993	contrast media			9020	SM
GONADORELIN	LUTREPULSE	11/08/1993	pituitary and hypothalamic hormones and analogues	01/10/1995	ovarian hyperstimulation	781	SM
ITRACONAZOLE	SPORANOX	17/08/1993	antimycotics for systemic use	2001-05-09; 2003-01-30; 2005-09-13	heart failure and pulmonary edema; don't use with ergotamine and dihydroergotamine containing drugs; may cause hypoventilation if used with fentanyl transdermal system	2822	SM
FLUTICASON	FLONASE	07/09/1993	nasal preparations	22/01/2004	increase risk of Cushing's if used with ritonavir	3789	SM
JAPANESE ENCEPHALITIS VIRUS VACCINE	JE-VAX	10/09/1993	vaccines			898	B
RAMIPRIL	ALTACE	08/10/1993	agents acting on the renin-angiotensin system	1997-07-01; 2006-06-29; 2014-02-04	bronchospasm; increased risk of birth defects; don't combine with aliskiren or ARBs	1362	SM
PIRBUTEROL	MAXAIR	05/11/1993	drugs for obstructive airway diseases			8932	SM
TERLIPRESSIN	SYNAREL	05/11/1993	pituitary and hypothalamic hormones and analogues	01/10/1995	myalgia, palpitation	695	SM
ISOSORBIDE-5 MONOHYDRATE	ISMO	01/12/1993	cardiac therapy			8906	SM
TINZAPARIN	LOGIPARIN	01/12/1993	antithrombotic agents	14/10/2010	increased mortality in elderly with renal impairment	6161	SM
PREDNICARBATE	DERMATOP	22/12/1993	corticosteroids, dermatological preparations			8885	SM
TRIMETREXATE	NEUTREXIN	24/12/1993	antiprotazoals			8883	SM
DORNASE ALFA	PULMOZYME	30/12/1993	cough and cold preparations			8877	B
FLUVASTATIN	LESCOL	31/12/1993	lipid modifying agents	2005-07-12; 2013-01-24	rhabdomyolysis; increased risk of diabetes	4211	SM
VIGABATRIN	SABRIL	14/01/1994	antiepileptics	01/10/1997	ophthalmological abnormalities	1356	SM
ALCLOMETASONE	ALDERM	01/02/1994	corticosteroids, dermatological preparations			8844	SM
ACITRETIN	SORIATANE	10/02/1994	antipsoriatics			8835	SM
LOPRIMIDE	ULTRAVIST	16/03/1994	contrast media			8801	SM
ETODOLAC	LODINE	18/03/1994	antiinflammatory and antirheumatic products			8799	SM
NABUMETONE	RELAFEN	18/03/1994	antiinflammatory and antirheumatic products			8799	SM
BEZAFIBRATE	BEZALIP	28/03/1994	lipid modifying agents			8789	SM
ANTITHROMBIN III	THROMBATE III	31/03/1994	antithrombotic agents			8786	B
GABAPENTINE	NEURONTIN	07/04/1994	antiepileptics			8779	SM
PIPERACILLIN + TAZOBACTAM	TAZOCIN	07/04/1994	antibacterials for systemic use	22/01/2004	associated with false positive assay	3577	SM
LEVOLEUCOVORIN	ISOVORIN	27/04/1994	all other therapeutic products			8759	SM
MIVACURIUM	MIVACRON	27/04/1994	muscle relaxants			8759	SM
NEFAZODONE	SERZONE	27/04/1994	psychoanaleptics	1996-04-01; 1999-07-01; 2001-06-01; 2003-01-30	central nervous system reactions; hepatotoxicity; serious and severe hepatic events; don't use with ergotamine and dihydroergotamine containing drugs	705	27/11/2003 hepatotoxicity 3501
VINORELBINE	NAVELBINE	10/05/1994	antineoplastic agents			8746	SM

GADODIAMIDE	OMNISCAN	18/05/1994	contrast media	2007-03-09; 2013-11-14; 2017-01-05	nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy; ; nephrogenic systemic fibrosis; may accumulate in brain	4678	SM
AZITHROMYCIN	ZITHROMAX	24/05/1994	antibacterials for systemic use	1997-10-01; 1999-01-01; 2006-10-03; 2013-05-14	iatrogenic hepatitis; convulsions; aggravation of myasthenia; risk of potentially fatal arrhythmia	1226	SM
HEPATITIS A VACCINE	HAVRIX	17/06/1994	vaccines			8708	B
SARGRAMOSTIM	PROKINE	23/06/1994	immunostimulants			8702	B
GRANISETRON	KYTRIL	14/07/1994	antiemetics and antinauseants	14/05/2014	potential risk of serotonin syndrome	7244	SM
VENLAFAXINE	EFFEXOR	18/07/1994	psychoanaleptics	1998-04-01; 2003-08-22; 2004-01-01; 2004-06-03; 2004-08-09; 2006-03-10; 2008-10-23; 2011-02-16	cardiac vasospasm; safety and effectiveness not established in pediatric patients; increased risk of self-harm; increased risk of self-harm; harm to newborn if mother taking; serious lung disorder in newborn; increased risk of fatal outcome in overdose compared to SSRI; serotonin toxicity if used in combination with methylene blue	1353	SM
FORMESTANE	LENTARON	25/08/1994	endocrine therapy			8639	SM
ALDESLUKIN	PROLEUKIN	15/09/1994	immunostimulants			8618	B
PERINDOPRIL	COVERSYL	21/09/1994	agents acting on the renin-angiotensin system	1997-07-01; 2006-06-29; 2014-02-04	bronchospasm; increased risk of birth defects; don't combine with aliskiren or ARBs	1014	SM
ROCURONIUM	ZEMURON	27/09/1994	muscle relaxants			8606	SM
SOMATOSTATIN	STILAMIN	27/09/1994	pituitary and hypothalamic hormones and analogues	02/06/2008	marked increase in hepatic enzymes	4997	SM
TORSEMIDE	DEMADEX	27/09/1994	diuretics			8606	SM
DALTEPARIN	FRAGMIN	30/09/1994	antithrombotic agents	01/04/2003	dosage change pre-hip surgery	3105	SM
FOSCARNET	FOSCAVIR	30/09/1994	antivirals for systemic use			8603	SM
SUPROFEN	PROFENAL	30/09/1994	antiinflammatory and antirheumatic products			8603	SM
DANAPAROID	ORGARAN	05/10/1994	antithrombotic agents			8598	SM
IODIXANOL	VISIPAQUE	25/10/1994	contrast media	24/04/2017	hypothyroidism	8217	SM
SALMETEROL	SEREVENT	25/10/1994	drugs for obstructive airway diseases	1995-04-01; 2003-09-04; 2005-09-07	don't use as acute therapy; risk of increased mortality by adding salmeterol to usual asthma therapy; risk of increased mortality by adding salmeterol to usual asthma therapy	158	SM
LAMOTRIGINE	LAMICTAL	21/11/1994	antiepileptics	1995-07-01; 1998-01-01; 2004-09-27; 2006-08-01	serious dermatological events; severe cutaneous reactions; concomitant use of hormonal contraceptives may significantly decrease serum lamotrigine levels; increased risk of non-syndromic oral clefts	222	SM
BISOPROLOL	MONOCOR	13/12/1994	beta blocking agents			8529	SM

Supplementary Table A2: New Active Substances approved 1995-1999

Generic name	Brand name	Date of Notice of Compliance (market approval)	Anatomical Therapeutic Chemical 2nd level	Dates of safety warnings	Reason for safety warning	Days from NOC to first safety warning	Date of withdrawal	Reason for withdrawal	Days from NOC to withdrawal	Biologic (B) or Small Molecule (SM)
Levocarnitine	Carnitor	19/01/1995	Other alimentary tract and metabolism products	2001/09/10	Do not use oral formulation for prolonged periods in patients with ESRD as major metabolites will accumulate	2426				SM
Adapalene	Differin	24/01/1995	anti-acne preparations			8487				SM
Bambuterol	Bambec	07/02/1995	drugs for obstructive airway diseases			8473				SM
Dexrazoxane	Zinecard	07/02/1995	all other therapeutic products			8473				SM
Losoxantrone	Bianda	19/02/1995	antineoplastic agents			8461				SM
Carvedilol	Dilatrend	27/02/1995	beta blocking agents			8453				SM
Carvedilol	Kredex	27/02/1995	beta blocking agents			8453				SM
Naltrexone	Revia	23/03/1995	other nervous system drugs			8412				SM
Cefprozil	Cefzil	29/03/1995	antibacterials for systemic use			8423				SM
Halofantrine	Halfan	29/03/1995	antiprotozoals			8423				SM
Zuclopenthixol	Clopixol	24/04/1995	psycholeptics	2011/06/15	Potential risk of abnormal muscle movements and withdrawal symptoms in newborns	5896				SM
Zuclopenthixol	Clopixol acuph	24/04/1995	psycholeptics	2011/06/15	Potential risk of abnormal muscle movements and withdrawal symptoms in newborns	5896				SM
Zuclopenthixol	Clopixol depot	24/04/1995	psycholeptics	2011/06/15	Potential risk of abnormal muscle movements and withdrawal symptoms in newborns	5896				SM
Ceftibuten	Cedax	09/05/1995	antibacterials for systemic use			8382				SM
Lansoprazole	Prevacid	12/05/1995	drugs for acid related disorders	2012-02-16; 2012-10-19; 2013-04-04	Possible association with increased risk of clostridium difficile diarrhea; When used with methotrexate, increase in methotrexate side effects; potential risk of bone fractures	6124				SM
Cefepime	Maxipime	02/06/1995	antibacterials for systemic use			8358				SM
Sermorelin	Geref	08/06/1995	diagnostic agents			8352				SM
Interferon Beta-1B	Betaseron	19/07/1995	immunostimulants	2003/12/04	Hepatotoxicity	2060				B
Famciclovir	Famvir	31/07/1995	antivirals for systemic use			8299				SM
Cefpodoxime	Orelox	22/08/1995	antibacterials for systemic use			8277				SM
Sevoflurane	Sevorane	18/09/1995	anesthetics	2017/12/22	May potentially lead to neurodevelopmental disorders in children	8131				SM
Losartan	Cozaar	28/09/1995	agents acting on the renin-angiotensin system			8240				SM
Iotrolan	Osmovist 280	04/10/1995	contrast media			8234				SM
Bicalutamide	Casodex	02/11/1995	endocrine therapy	2003/08/18	Accelerated deaths in patients with prostate cancer	2846				SM
Acarbose	Prandase	15/11/1995	drugs used in diabetes			8192				SM
Mycophenolate	Cellcept	15/11/1995	immunosuppressants	2006-10-13; 2009-06-03; 2009-12-21; 2016-01-18	Increased incidence of acute rejection in cardiac transplantation in patients switched to mycophenolate and sirolimus; pure red cell aplasia; pure red cell aplasia; teratogenicity warning added to labelling	3985				SM
Tacrolimus	Prograf	06/12/1995	immunosuppressants	1998/01/01	QT prolongation	757				SM

Lamivudine	3TC	08/12/1995	antivirals for systemic use	2003/10/17	Lamivudine and abacavir in combination with tenofovir should not be used as triple therapy	2870			SM
Alendronate	Fosamax	20/12/1995	drugs for treatment of bone diseases	1998-04-01; 2010-10-14; 2011-12-19	Esophagitis; femur fracture; atypical femur fracture	833			SM
Tetrabenzazine	Nitoman	29/12/1995	other nervous system drugs			8148			SM
Iron dextran	Dexferrum	09/01/1996	antianemic preparations			8137			SM
Rimexolone	Vexol	17/01/1996	corticosteroids for systemic use			8129			SM
Measles virus vaccine/Rubella virus vaccine	Moru-Viraten	26/02/1996	vaccines			8089			B
Ferumoxsil	Gastromark	15/03/1996	contrast media			8071			SM
Saquinavir	Saquinavir	22/03/1996	antivirals for systemic use	1997-01-01; 1997-07-04; 2005-02-10; 2010-04-14; 2010-10-27	Increased bleeding in hemophilia; hyperglycemia & diabetes; rifampin should not be administered to patients also receiving saquinavir/ritonavir; significant dose-dependent prolongation of QT & PR intervals; QT/PR prolongation & need for ECG monitoring	285			SM
Stavudine	Zerit	26/03/1996	antivirals for systemic use	2002/03/06	Symptoms mimicking Guillain-Barre	2171			SM
Acellular pertussis vaccine adsorbed	Acel-P	29/03/1996	vaccines			8057			B
Amifostine	Ethyol	25/04/1996	all other therapeutic products	2002/03/12	Severe cutaneous reactions	2147			SM
Dorzolamide	Trusopt	25/04/1996	ophthalmologicals	1998/04/01	cardiovascular, GI, visual and hearing, CNS, skin disorders	706			SM
Valacyclovir	Valtrex	01/05/1996	antivirals for systemic use			8024			SM
Quinagolide	Norprolac	25/06/1996	other gynecologicals			7969			SM
Meropenem	Merrem	02/07/1996	antibacterials for systemic use			7962			SM
Abciximab	Reopro	04/07/1996	antithrombotic agents	1999/07/01	thrombocytopenia	1092			B
Pantoprazole	Panto-Byk	05/07/1996	drugs for acid related disorders	1998-10-01; 2009-08-14; 2012-02-16; 2012-10-19; 2013-04-04	Chest pain; potential reduction in the level of clopidogrel's active metabolite; possible association with increased risk of clostridium difficile diarrhea; when used with methotrexate, increase in methotrexate side effects; potential risk of bone fractures	818			SM
Dexfenfluramine	Redux	29/07/1996	antiobesity preparations	1996-10-21; 1997-01-01; 1997-10-01	Primary pulmonary hypertension; primary pulmonary hypertension; cardiac valvulopathy	84	15/09/1997	cardiac valve damage	413 SM
Palmitic acid/Galactose	Levovist	31/07/1996	diagnostic agents			7933			SM
Anastrozole	Arimidex	01/08/1996	endocrine therapy			7932			SM
Ritonavir	Norvir	14/08/1996	antivirals for systemic use	1997-01-01; 1997-07-04; 2000-04-06; 2004-01-22	Increased bleeding in hemophilia; hyperglycemia & diabetes; interactions with St. John's Wort; ritonavir can greatly increase fluticasone propionate plasma concentrations	140			SM
Fleroxacin	Megalone	21/08/1996	antibacterials for systemic use			7912			SM

Reviparin	Clivarine	10/09/1996	antithrombotic agents			7892	SM
Raltitrexed	Tomudex	12/09/1996	antineoplastic agents			7890	SM
Indinavir	Crixivan	13/09/1996	antivirals for systemic use	1997-01-01; 1997-07-04; 2000-01-01; 2000-04-06	Increased bleeding in hemophilia; hyperglycemia & diabetes; paronychia; interactions with St. John's Wort	110	SM
Insulin lispro	Humalog	08/10/1996	drugs used in diabetes			7854	B
Dirithromycin	Dynabac	28/10/1996	antibacterials for systemic use			7844	SM
Olanzapine	Zyprexa	28/10/1996	psycholeptics	1998-07-01; 1999-04-01; 2000-07-01; 2004-03-10; 2005-06-22; 2011-06-15	hematological reactions; priapism; various suspected serious reactions; increased risk of cerebrovascular adverse events in elderly with dementia; increased risk in all-cause mortality in elderly patients with behavioural disorders; potential risk of abnormal muscle movements and withdrawal symptoms in newborns	611	SM
Nalmefene	Revex	06/11/1996	other nervous system drugs			7835	SM
Zolpidem	Ambien	20/11/1996	psycholeptics	2011-11-30; 2014-01-03	Association with complex sleep behaviours (warning issued for Sublinox); reduction in dosage	5488	SM
Desflurane	Suprane	03/12/1996	anesthetics	2017/12/22	May potentially lead to neurodevelopmental disorders in children	7689	SM
Diphtheria, tetanus & acellular pertussis vaccine	Infanrix	17/12/1996	vaccines			7794	B
Cisatracurium	Nimbex injecti	18/12/1996	muscle relaxants			7793	SM
Gemcitabine	Gemzar	23/12/1996	antineoplastic agents			7788	SM
Remifentanyl	Ultiva injection	24/12/1996	anesthetics			7787	SM
Ropivacaine	Naropin injecti	24/12/1996	anesthetics			7787	SM
Tiludronate	Skelid	06/02/1997	drugs for treatment of bone diseases			7743	SM
Imiglucerase	Cerezyme	12/02/1997	Other alimentary tract and metabolism products			7737	B
Atorvastatin	Lipitor	19/02/1997	lipid modifying agents	2013/01/24	Small increased risk of diabetes	5818	SM
Tazarotene	Tazorac Gel	25/02/1997	antipsoriatics			7724	SM
Epoprostenol	Flolan	06/03/1997	antithrombotic agents			7715	SM
Formoterol	Foradil dry pov	06/03/1997	drugs for obstructive airway diseases	2005/09/07	Increased risk of asthma-related deaths in patients who also used salmeterol	3107	SM
Topiramate	Topamax	06/03/1997	antiepileptics	2001-09-13; 2003-07-11; 2004-01-12	Acute myopia & secondary angle closure glaucoma; oligohydrosis & hyperthermia; metabolic acidosis	1652	SM
Praziquantel	Biltricide	07/03/1997	anthelmintics			7714	SM
Molgramostim	Leucomax	10/03/1997	immunostimulants			7711	B
Fosphenytoin	Cerebyx injecti	20/03/1997	antiepileptics			7701	SM
Coagulation factor IX	Benefix	21/03/1997	antihemorrhagics			7700	B
Butenafine	Dr. Scholl's ath	15/04/1997	antifungals for dermatological use			7675	SM
Topotecan	Hycamtin	15/04/1997	antineoplastic agents			7675	SM

Troglitazone	Rezulin	09/05/1997	drugs used in diabetes			15/03/2000	Hepatotoxicity (approved in Canada but never marketed because of dispute with PMPRB - removed from US market in March 2000 & ? NOC revoked in Canada then)	1041	SM	
Trandolapril	Odrik	15/05/1997	agents acting on the renin-angiotensin system			7645			SM	
Dolasetron	Anzemet	21/05/1997	antiemetics and antinauseants	2006-06-23; 2011-04-26	Contraindicated in those under 18 for the prevention & treatment of post-operative nausea; withdrawal of IV form due to risk of arrhythmias	3320	21/04/2014	Risk of arrhythmias	6179	SM
Letrozole	Femara	21/05/1997	endocrine therapy			7639				SM
Follitropin alfa	Gonal-F	06/06/1997	sex hormones and modulators of the genital system	1999/10/01	sleep disorder	847				B
Fexofenadine	Allegra	11/06/1997	antihistamines for systemic use			7618				SM
Latanoprost	Xalatan	16/06/1997	ophthalmologicals	199-07-01	cardiovascular reactions	380				SM
Carbetocin	Duratocin	24/06/1997	pituitary and hypothalamic hormones and analogues			7605				SM
Follitropin beta	Puregon	02/07/1997	sex hormones and modulators of the genital system			7597				B
Kit for preparation of indium in 111 imciromab pentetate	Myoscint	02/07/1997	diagnostic radiopharmaceuticals			7597				SM
Irinotecan	Camptosar	04/07/1997	antineoplastic agents	2001/05/11	Increased mortality in clinical trials	1407				SM
Cytomegalovirus immune globulin	Cytogam	01/08/1997	immune sera and immunoglobulins			7567				B
Oxiconazole	Oxizole	08/08/1997	antifungals for dermatological use			7560				SM
Donepezil	Aricept	12/08/1997	psychoanaleptics	1998-07-01; 2015-01-21	Expected and unexpected ADRs; rhabdomyolysis; neuroleptic malignant syndrome	323				SM
Ropinirole	Requip	19/08/1997	anti-parkinson drugs			7549				SM
Respiratory syncytial virus immune globulin	Respigam	20/08/1997	immune sera and immunoglobulins			7548				B
Ibandronate	Bondronat	27/08/1997	drugs for treatment of bone diseases			7541				SM
Glatiramer	Copaxone for i	04/09/1997	immunostimulants			7533				SM
Arcitumomab	CEA-Scan	16/09/1997	diagnostic radiopharmaceuticals			7521				SM
Olopatadine	Patanol	16/09/1997	nasal preparations			7521				SM
Tolcapone	Tasmar	08/10/1997	anti-parkinson drugs				20/11/1998	Hepatotoxicity	408	SM
Zafirlukast	Accolate	21/10/1997	drugs for obstructive airway diseases	1999-10-01; 2002-12-18; 2004-04-14	eosinophilic conditions; hepatotoxicity; hepatotoxicity	710				SM
Valsartan	Diovan	03/11/1997	agents acting on the renin-angiotensin system			7473				SM

Levofloxacin	Levaquin	14/11/1997	antibacterials for systemic use	2011-11-07; 2012-03-09; 2017-01-23	Worsening of symptoms in myasthenia gravis; worsening of symptoms in myasthenia gravis; disabling and persistent serious adverse reactions including tendinopathy, peripheral neuropathy, and central nervous disorders	5106			SM
Anagrelide as hydrochloride	Agrylin	19/11/1997	antineoplastic agents			7457			SM
Pegaspargase	Oncaspar	19/11/1997	antineoplastic agents			7457			B
Brimonidine	Alphagan ophth	24/11/1997	ophthalmologicals			7452			SM
Nadroparin	Fraxiparine	27/11/1997	antithrombotic agents			7449			SM
Quetiapine	Seroquel	02/12/1997	psycholeptics	2005-06-22; 2011-06-15	Increased risk in all-cause mortality in elderly patients with behavioural disorders; potential risk of abnormal muscle movements and withdrawal symptoms in newborns	2759			SM
Bicisate	OncoScint	16/01/1998	diagnostic radiopharmaceuticals			7399			SM
Pramipexole	Mirapex	28/01/1998	anti-parkinson drugs			7387			SM
Interferon Beta-1A	Rebif	05/02/1998	immunostimulants	2003/12/04	Hepatotoxicity	2128			B
Emedastine	Emadine ophth	16/02/1998	ophthalmologicals			7366			SM
Cerivastatin	Baycol	18/02/1998	lipid modifying agents	2001/07/16	Rhabdomyolysis	1244	08/08/2001	Rhabdomyolysis	1267
Gadolinium (III)	Gadolite	08/04/1998	contrast media			7317			SM
Grepafloxacin	Raxar	09/04/1998	antibacterials for systemic use				26/10/1999	Cardiac arrhythmias	565
Bupropion	Wellbutrin SR	28/04/1998	psychoanalectics	2001-07-03; 2004-06-08; 2004-08-09; 2006-03-10; 2013-05-30	Reduction in risk of seizures and drug interactions; risk of self harm; complications in infants if used in pregnancy; persistent pulmonary hypertension of the newborn; consider nicotine replacement therapy first	1162			SM
Naratriptan	Amerge	28/04/1998	analgesics			7297			SM
Irbesartan	Avapro	01/06/1998	agents acting on the renin-angiotensin system			7263			SM
Tamsulosin	Flomax	01/06/1998	urologicals	2005/10/14	Intraoperative floppy iris syndrome	2692			SM
Montelukast	Singulair	17/06/1998	drugs for obstructive airway diseases	1999/10/01	eosinophilic conditions	471			SM
Lexidronam	Quadramet	22/06/1998	therapeutic radiopharmaceuticals			7242			SM
Delavirdine	Rescriptor	22/07/1998	antivirals for systemic use			7212			SM
Miglitol	Glyset	22/07/1998	drugs used in diabetes			7212			SM
Nelfinavir	Viracept	11/08/1998	antivirals for systemic use			7192			SM
Zolmitriptan	Zomig	24/08/1998	analgesics			7179			SM
Capecitabine	Xeloda	31/08/1998	antineoplastic agents			7172			SM
Nevirapine	Viramune	04/09/1998	antivirals for systemic use	2000-11-10; 2001-02-26; 2004-02-20	Severe life-threatening & fatal hepatotoxicity; strenthened warnings about serious liver & skin toxicity; subgroup of women at considerably higher risk of hepatotoxicity	798			SM

Clopidogrel	Plavix	07/10/1998	antithrombotic agents	2009-08-14; 2011-09-22; 2015-07-31	Use with PPIs can decrease effectiveness of clopidogrel; use with PPIs can decrease effectiveness of clopidogrel; hypoglycemia possible if used with repaglinide	3964	SM
Brinzolamide	Azopt ophthal	23/10/1998	ophthalmologicals			7119	SM
Raloxifene	Evista	06/11/1998	sex hormones and modulators of the genital system	2006/05/18	Increased mortality due to stroke	2750	SM
Candesartan	Atacand	20/11/1998	agents acting on the renin-angiotensin system			7091	SM
Tolterodine	Detrol	20/11/1998	urologicals			7091	SM
Lipoprotein-OspA antigen recombinant	Lymerix	02/12/1998	vaccines			7079	B
Varicella vaccine	Varivax	02/12/1998	vaccines			7070	B
Alatrofloxacin	Trovan (IV)	04/12/1998	antibacterials for systemic use	2017/01/23	Disabling and persistent serious adverse reactions including tendinopathy, peripheral neuropathy, and central nervous disorders	6625	SM
Trovafoxacin	Trovan (tablets)	04/12/1998	antibacterials for systemic use			22/11/2001	Hepatotoxicity 1084 SM
Toremifene	Fareston	14/12/1998	endocrine therapy			7067	SM
Becaplermin gel	Regranex	30/12/1998	preparations for treatment of wounds and ulcers			7051	SM
Tizanidine	Zanaflex	25/01/1999	muscle relaxants			7025	SM
Penciclovir	Denavir	02/02/1999	antivirals for systemic use			7017	SM
Cefdinir	Omnicef	05/02/1999	antibacterials for systemic use			7014	SM
Citalopram	Celexa	05/02/1999	psychoanaleptics	2000-07-01; 2004-05-26; 2004-08-09; 2006-03-10; 2011-10-13; 2012-01-25	Interaction with clarithromycin; risk of self harm; complications in infants if used in pregnancy; persistent pulmonary hypertension of the newborn; heart related safety; QT prolongation	512	SM
Recombinant factor	Niastase	12/02/1999	antihemorrhagics			7007	B
Methacholine	Methacholine	25/02/1999	other diagnostic agents			6994	SM
Modafinil	Alertec	26/02/1999	psychoanaleptics	18/12/2007	Serious rash, allergic reactions & mental problems	3217	SM
Sildenafil	Viagra	08/03/1999	urologicals	2000-07-01; 2007-05-06	Cardiac problems; serious visual disturbances	481	SM
Recombinant-methi	Infergen	11/03/1999	immunostimulants			6980	B
Efavirenz	Sustiva	19/03/1999	antivirals for systemic use			6972	SM
Repaglinide	Gluconorm	06/04/1999	drugs used in diabetes	2003-06-16; 2003-08-08; 2015-07-31	Should not be used in combination with gemfibrozil risk of severe and prolonged hypoglycemia; should not be used in combination with gemfibrozil; hypoglycemia possible if used with clopidogrel	1532	SM
Fosfomycin	Monurol	12/04/1999	antibacterials for systemic use			6948	SM
Celecoxib	Celebrex	14/04/1999	antiinflammatory and antirheumatic products	2000-01-01; 2002-05-13; 2004-12-20; 2005-09-21	various suspected ADRs; standard contraindications for NSAIDs added to Product Monograph for celecoxib; increased cardiovascular risk; cardiovascular risks	262	SM
Triptorelin	Trelstar	06/05/1999	endocrine therapy			6924	SM

Ancestim	Stemgen	20/05/1999	immunostimulants			6910			B
Orlistat	Xenical	03/06/1999	antiobesity preparations	01/01/2000	pancreatitis	212			SM
Abacavir	Ziagen	04/06/1999	antivirals for systemic use	2003-10-17; 2008-06-18	Lamivudine and abacavir in combination with tenofovir should not be used as triple therapy; risk of cardiac events	1596			SM
Alitretinoin	Panretin	11/06/1999	antineoplastic agents			6888			SM
Eptifibatide	Integrilin	11/06/1999	antithrombotic agents			6888			SM
Eprosartan	Teveten	09/07/1999	agents acting on the renin- angiotensin system			6860			SM
Cidofovir	Vistide	13/07/1999	antivirals for systemic use			6856			SM
Rizatriptan	Maxalt	16/07/1999	analgesics			6853			SM
Trastuzumab	Herceptin	13/08/1999	antineoplastic agents	21/04/2009	Oligohydramnios	3539			B
Telmisartan	Micardis	16/08/1999	agents acting on the renin- angiotensin system			6822			SM
Risedronate	Actonel	18/08/1999	drugs for treatment of bone diseases	2010-10-14; 2011-12-19	Femur fracture; atypical femur fracture	4075			SM
Tirofiban	Aggrastat	19/08/1999	antithrombotic agents			6819			SM
Icodextrin	Extraneal	17/09/1999	blood substitutes and perfusion solutions			6790			SM
Ioxilan	Oxilan	05/10/1999	contrast media			6722			SM
Varicella zoster vacc	Varilrix	13/10/1999	vaccines			6764			B
Rofecoxib	Vioxx	25/10/1999	antiinflammatory and antirheumatic products	15/04/2002	Increase in cardiovascular risk	903	30/09/2004	Increased cardiovascula r events	1802 SM
Temozolomide	Temodal	25/10/1999	antineoplastic agents	07/05/2014	Risk of liver problems	5308			SM
Zanamivir	Relenza	02/11/1999	antivirals for systemic use	01/10/2000	various suspected ADRs	334			SM
Melanoma theraccir	Melacine	04/11/1999	immunostimulants			6742			B
Gadobutrol	Gadovist	08/11/1999	contrast media	05/01/2017	May accumulate in brain	6268			SM
Dalfopristin	Synercid	10/12/1999	antibacterials for systemic use			6706			SM
Oseltamivir	Tamiflu	23/12/1999	antivirals for systemic use	2000-10-01; 2004-02-09	Various suspected ADRs; don't use in children under 1	282			SM

Supplementary Table A3: Distribution of Unique New Active Substances in Anatomic, Therapeutic and Chemical Groups

ATC second level group	1990-1994	1995-1999
Agents acting on the renin-angiotensin system	7	7
All other therapeutic products	3	2
Analgesics	2	3
Anesthetics	1	4
Anti-acne preparations	0	1
Anti-Parkinson drugs	2	3
Antianemic preparations	1	1
Antibacterials for systemic use	11	14
Antibiotics and chemotherapeutics for dermatological use	2	0
Antidiarrheals, intestinal anti-inflammatory/antiinfective agents	2	0
Antiemetics and antinauseants	2	1
Antiepileptics	3	2
Antifungals for dermatological use	2	2
Antihelmintics	1	1
Antihemorrhagics	1	2
Antihistamines for systemic use	2	1
Antihypertensives	1	0
Antiinflammatory and antirheumatic products	6	2
Antimycobacterials	1	0
Antimycotics for systemic use	2	0
Antineoplastic agents	7	11
Antiobesity preparations	0	2
Antiprotozoals	3	1
Antipsoriatics	2	1
Antithrombotic agents	7	7
Antivirals for systemic use	3	16
Beta blocking agents	2	1
Bile and liver therapy	1	0
Blood substitutes and perfusion solutions	1	1
Calcium channel blockers	4	0
Cardiac therapy	4	0

Contrast media	7	5
Corticosteroids, dermatological preparations	4	0
Corticosteroids for systemic use	0	1
Cough and cold preparations	1	0
Diagnostic agents	0	2
Diagnostic radiopharmaceuticals	1	3
Diuretics	2	0
Drugs for acid related disorders	0	2
Drugs for obstructive airway diseases	3	4
Drugs for treatment of bone diseases	2	4
Drugs used in diabetes	0	5
Endocrine therapy	2	5
Gynecological antiinfectives and antiseptics	1	0
Immune sera and immunoglobulins	1	2
Immunostimulants	4	7
Immunosuppressants	0	2
Lipid modifying agents	5	2
Muscle relaxants	4	2
Nasal preparations	2	1
Ophthalmologicals	4	5
Other alimentary tract and metabolism products	0	2
Other diagnostic agents	0	1
Other drugs for disorders of the musculo-skeletal system	1	0
Other gynecologicals	0	1
Other nervous system drugs	1	3
Other respiratory system products	2	0
Pituitary and hypothalamic hormones and analogues	4	1
Preparations for treatment of wounds and ulcers	1	1
Psychoanaleptics	6	4
Psycholeptics	5	4
Sex hormones and modulators of the genital system	2	3
Therapeutic radiopharmaceuticals	0	1
Urologicals	1	3

Vaccines	7	6
Vasoprotectives	1	0

No difference in the distribution of the NAS into different therapeutic groups in the two time periods, $p = 0.1322$ (Chi-square)