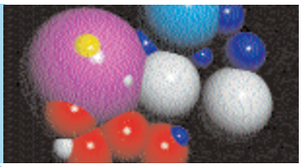

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The aim of this review, following the others about the new "Molecular Entities" (NME) approved by the Food and Drug Administration (FDA) in the years 1998-2002 (1), is to survey the NME approved by the FDA in the year 2003 (i.e., those not previously marketed in the United States of America). Herein the drugs subjected to "Priority Review" (i.e., those representing therapeutic gains over existing therapies) (9 NME, 57 references) will be considered. Some of these NME were subjected to an accelerated approval: this program helps make products for serious or life-threatening diseases available earlier in the development process. The FDA bases approval on a promising effect of the drug that can be observed significantly sooner than can long-term clinical benefits; in addition, sponsors perform additional studies to demonstrate these benefits (2). As for the drugs subjected to "Standard Review" (i.e., those having similar therapeutic properties when compared to drugs already on the market) (12 NME), only basic information (product, sponsor, date approved, indication, structural formula and availability in Italy) will be given (3). The NME also include orphan drugs, which are considered those for use in patient populations of 200,000 or fewer, for which the FDA administers a program that provides incentives for development: sponsors, in fact, receive inducements that include seven-year marketing exclusivity, tax credits for the product-associated clinical research, research design assistance and grants of up to $200,000 per year (2).

New Molecular Entities Approved in 2003 with Priority Review

In order to offer an overview of the subject, the drugs have been grouped into therapeutic classes, as can be seen in Figure 1. Anticancer and antiviral drugs are present (as in 1998-2002), as is an antibacterial drug (as in 1999, 2000) because of the great interest in the related diseases. In addition an antiemetic, a hormone antagonist and an antidote are reported in FDA-approved NME.

Antiviral drugs

Fuzeon™ (Trimeris/Roche)
Enfuvirtide, 90 mg, injection (4)
Indication: fusion inhibitor for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

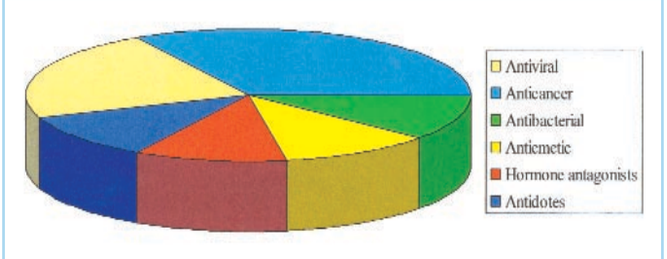


Figure 1 - Therapeutic classes of NME approved by "priority review"

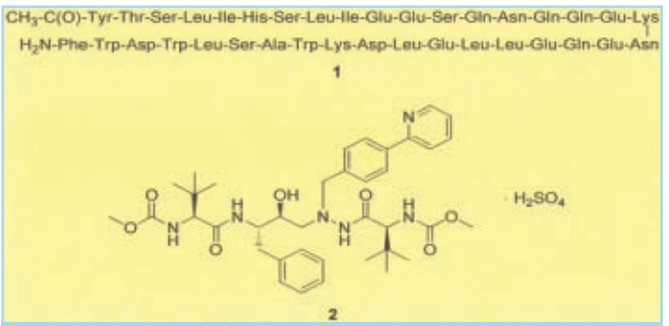


Figure 2 - Antiviral drugs

Date approved: 13-03-2003 (accelerated approved) (available also in Italy (5))

Reyataz® (Bristol-Myers Squibb)
Atazanavir sulfate, 100, 150 & 200 mg, capsule (6)
Indication: once-daily protease inhibitor (PI) for use in combination with other anti-retroviral agents for the treatment of patients with HIV-1 infection.
Date approved: 20-06-2003

The human immunodeficiency virus (HIV) types I and II cause the destruction of CD4 cells in their hosts, resulting in the development of AIDS (7). At present, there is no effective treatment to cure this disease. The best currently available regimen, highly active antiretroviral therapy (HAART), which includes a cocktail of two or more different anti-HIV agents (reverse transcriptase (RT) and PI), has led to dramatically improved survival for many HIV-infected individuals, but ultimately fails to control the disease in half of treated patients (8). HIV-1 enters into the target cells by fusion of the viral envelope with the target cell membrane, leading to the release of the viral genetic material into the cell. The fusion events are mediated by HIV-1 envelope glycoprotein (Env) surface subunit gp120 and the transmembrane subunit gp41 (9). In the last years six PIs have been approved but these drugs require multiple daily doses, and are commonly associated with significant side effects that contribute to reduce compliance and the consequent increased risk of drug resistance emerging (10).
Enfuvirtide (**1**, Figure 2) is a 36-amino acid peptide synthesized as described in (11). **1** is the first of a new class of antiretroviral agents that block HIV-1 entry into the host cell by binding to the gp41 subunit of the HIV Env glycoprotein (4c, 12). In vitro and in vivo studies with **1** have demonstrated potent antiviral activity, also in patients with multi-drug resistant virus (4a).
Atazanavir sulfate (**2**, Figure 2) is a new azapeptide synthesized as described in (13). **2**, differing from other peptidomimetic PIs by its C-2 symmetric chemical structure, was designed based on X-ray studies of an enzyme-azapeptide complex (6a, 14) and through a lead identification study (15). **2** blocks the cleavage of viral *gag* and *gag-pol* precursors polyproteins into viral structural proteins, reverse transcriptase, integrase and protease, which results in the release of noninfectious and immature viral particles from cells infected by HIV-1 (6a, 16).

Anticancer drugs

Iressa™ (AstraZeneca)
Gefinitib, 250 mg, tablet (17)
Indication: epidermal growth factor receptor (EGFR) blocker for use as monotherapy in the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of both platinum-based and docetaxel chemotherapies.
Date approved: 05-05-2003 (accelerated approved)

The growth of NSCLC, which accounts for over 80% of all malignant lung tumors, is regulated by various growth factors, acting through their respective transmembrane receptors, such as EGFR (18), which represents an ideal target for development of newly targeted therapies (19). EGFR is a member of ErbB family of cell surface receptors which have an intracellular tyrosine kinase domain (17a). These receptors exist as inactive monomers: ligand binding determines a conformational change of the extracellular domain including receptor dimerization with consequent receptor activation, through a transphosphorylation of intracellular domain tyrosines (19a,b). These phosphorylated tyrosines serve as the binding sites for several signal transducers and adaptor molecules, which initiate a cascade of biochemical events resulting in cell proliferation (19a). The discovery of the structure of the EGFR and its ligands, their signal transduction pathways and their role in tumorigenesis has led to a focus on development of potential anticancer therapies that target these pathways including anti-receptor monoclonal antibodies as well as small-molecule tyrosine kinase inhibitors (17b, 20).
Gefinitib (**3**, Figure 3) is an anilinoquinazoline derivative synthesized as described in (21). **3** is a potent inhibitor of EGFR tyrosine phosphorylation by competing with adenosine triphosphate (22). **3** has a defined mode of binding, as suggested by its structure-activity relationship pattern where the quinazoline ring binds in the adenine pocket and the aniline ring binds in an adjacent lipophilic pocket (21, 23). It was suggested that **3** is effective only in lung cancer patients with tumors that are driven by activated forms of EGFR (24). **3** is also being studied in combination with trastuzumab in metastatic breast cancer, due to preclinical experiments showing a cooperative inhibitory effect from targeting both EGFR and HER2, another receptor included in ErbB family (25).

Plenaxis™ (Praecis)
Abarelix, 113 mg, injection (26)
Indication: gonadotropin releasing-hormone (GnRH) antagonist for the palliative treatment of men with advanced symptomatic prostate cancer, in whom luteinizing hormone-releasing hormone (LHRH) agonist therapy is not appropriate and who refuse surgical castration, and have risk of neurological compromise due to metastases, ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or severe bone pain from skeletal metastases persisting on narcotic analgesia.
Date approved: 25-11-2003
Prostate cancer is one of the most commonly diagnosed cancers in men, and is a major cause of cancer deaths (27). Analogs of LHRH known as GnRH are used in the treatment of conditions in which hormone modulation is beneficial to the resolution of the disease (26). The administration of an LHRH agonist causes an initial surge in testosterone levels, followed 3-4 weeks thereafter by inhibition of the production of LH and suppression of testosterone and dihydrotestosterone to target levels, so the use of agonists (or so-called superagonists, such as leuprolide and goserelin) leads to stimulation of LHRH receptors prior to their desensitization (26). LHRH antagonists, in contrast, produce a rapid and complete suppression of testosterone levels (26).
Abarelix (**4**, Figure 3) is a decapeptide synthesized as described in (28). **4**, developed as a sustained-release formulation for administration over prolonged periods of time, results in immediate inhibition of the hypothalamic-pituitary-gonadal axis (29). **4** belongs to third generation of GnRH antagonists, whose structural features are presented in (30).

Velcade® (Millennium) (orphan drug)
Bortezomib, 3.5 mg, injection (31)
Indication: proteasome inhibitor for use in the treatment of multiple myeloma (MM) patients who have received at least two prior therapies and demonstrated disease progression on the last therapy.
Date approved: 13-05-2003 (accelerated approved)

The proteasome is an abundant multi-enzyme complex that provides the main pathway for degradation of intracellular proteins in eukaryotic cells (32). The elimination of many key proteins by the proteasome is required for essential cellular processes, including cell-cycle progression, cell survival and cellular homeostasis. On the contrary, inhibition of the proteasome results in cell-cycle arrest or programmed cell death (31). The observation that malignant cells were more susceptible to the effects of proteasome inhibition than normal cells makes this a novel approach in cancer therapy (31). MM, a malignant B-cell tumour characterized by osteolytic bone lesions, is the second most common haematological cancer (after non-Hodgkin's lymphoma) (33). Treatment has relied predominantly on glucocoticoids as well as alkylating agents. Although these treatments improve survival (five-years survival is ~29%), the disease remains incurable (33).
Bortezomib (**5**, Figure 3) is a dipeptidyl boronic acid derivative synthesized as described in (34). **5** binds the 26S proteasome, a large protein complex that degrades ubiquitina-

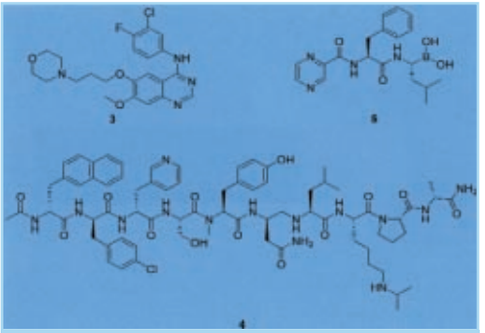
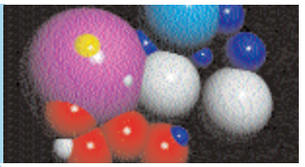


Figure 3 - Anticancer drugs



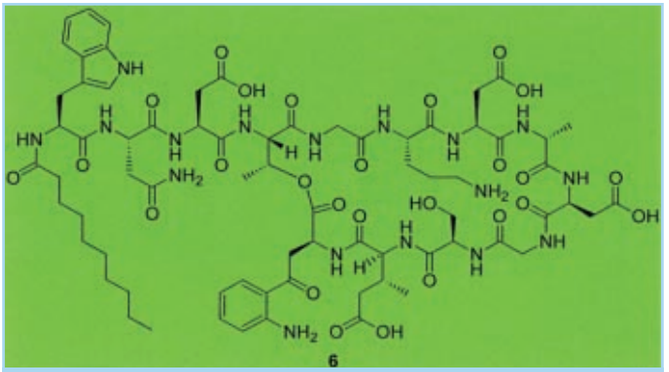


Figure 4 - Antibacterial drugs

ted proteins (35), so blocking the activation of nuclear factor-kB (33). **5** inhibits proteolysis by acting as reversible inhibitor, presumably forming a complex with the *N*-terminal threonin hydroxyl group in the chymotrypsin-like active site (34). **5** offers the advantages of reduced molecular weight and simplified synthesis, and exhibits extremely high selectivity for the proteasome over common serine proteases (34). In addition to **5**, there are promising therapies emerging for the treatment of MM, such as thalidomide, arsenic trioxide and oblimersen, an oligonucleotide antisense (33).

Antibacterial drugs

Cubicin™ (formerly *Cidecin*) (Cubist)
Daptomycin, 4 mg/kg/day, injection (36)
Indication: cyclic lipopetide antibacterial agent for the treatment of complicated skin and skin structure infections (cSSSIc) caused by susceptible strains of the Gram-positive microorganisms *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae* subsp. *equisimilis* and *Enterococcus faecalis* (vancomycin-susceptible strains only).
Date approved: 12-09-2003

An SSSI is defined as complicated if it requires surgical intervention and/or is known or suspected to involve deeper soft tissue layers of muscle and fascia (36). For empiric treatment of *Staphylococcus aureus* or *Streptococcus pyogenes* infection, an anti-staphylococcal penicillin such as oxacillin or nafcillin or a first-generation cephalosporin such as cefazolin has been a first choice (37). However, the increasing prevalence of methicillin-resistant *Staphylococcus aureus* strains (MRSA), which are also resistant to antistaphylococcal penicillins and cephalosporins, has led to an increased use of vancomycin (37). Since the appearance of vancomycin-resistant strains, two new antibiotics have been introduced, i.e. the streptogramin combination quinupristin/dalfopristin (1b) and linezolid (1d), but despite this there is a growing need to develop new antibiotics to combat the problem of resistance (38).

Daptomycin (**6**, Figure 4) is a cyclic lipopeptide antibiotic derived from enzymatic and chemical modifications of lipopeptide produced by *Streptomyces roseosporus* (39). Unlike many other antibiotics, **6** does not directly inhibit the cellular synthesis of proteins, the cell wall, DNA or RNA (40) but the binding of **6** to bacterial cells results in disruption of the membrane potential, so the synthesis of protein, DNA and RNA is inhibited by this phenomenon, leading to bacterial cell death (36, 41). As reported in (42), however, the exact mechanism through which **6** acts has not been determined (43).

Antiemetic drugs

Emend® (Merck)
Aprepitant, 80 & 125 mg, capsule (44)
Indication: oral substance P/neurokinin-1 receptor antagonist for use in combination with other antiemetic agents for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.
Date approved: 26-03-2003

There are three types of chemotherapy-induced nausea and vomiting (CINV): anticipatory, which is usually seen in patients who have previously experienced with CINV; acute and delayed defined as occurring within 24 hours or more than 16-24 hours after chemotherapy, respectively (44a). Delayed may persist for up to 7 days and is more difficult to treat because it is not as well understood as acute (44a). In chemoreceptor trigger zones (CTZs) several receptors have been identified, among which those of dopamine, serotonin and neurokinin (44a). Recently it was suggested that substance P, a tachykinin which acts through the neurokinin NK_1 receptor pathways, may also be involved in delayed CINV (44a). The goal in patients under chemotherapy regimen is prevention, because once present, CINV is very difficult to treat (44a). The current standard treatment of patients receiving moderately or highly emetogenic chemotherapy regimens for acute CINV is a therapy based to a 5-HT_3 receptor antagonist and a corticosteroid, but this combination is satisfactory only in acute CINV, not in delayed (44a).
Aprepitant (**7**, Figure 5) is a morpholine derivative synthesized as described in (45). **7** antagonises the effects of substance P in the CNS binding the NK_1 receptor in the brain. **7** in combination with ondansetron and dexamethasone is effective in the prevention of acute and delayed CINV after high-dose cisplatin, and produced higher response rate than the other drugs above-mentioned alone. This preventive efficacy is maintained across multiple cycles of chemotherapy (44a). Because **7** has a poor solubility in aqueous solutions, its *N*-phosphorylated prodrug is under study (46).

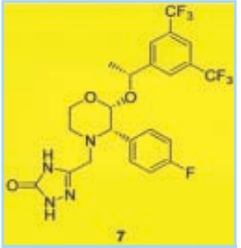


Figure 5 - Antiemetic drugs

Hormone antagonists

Somavert® (Pfizer) (orphan drug)
Pegvisomant, 10, 15 & 20 mg, injection (47)
Indication: human growth hormone (GH, somatotropin) receptor antagonist for the treatment of acromegaly in patients who have had an inadequate response to surgery and/or other medical therapies, or for whom these therapies are not appropriate.
Date approved: 25-03-2003

Figure 6 - Hormone antagonists

GH, a peptide hormone secreted from the anterior pituitary, is particularly important for normal growth and development. Secretion is stimulated by the growth hormone-releasing hormone (GHRH) and inhibited by somatostatin, so it is regulated by the interaction of these hormones (47). The presence of GH into the bloodstream produces in the liver, insuline-like growth factor-1 (IGF-1) a mediator of many effects of GH on promoting growth of bone and other tissues (47). Acromegaly is a hormonal disorder caused by prolonged overproduction of GH; in over 90% of patients this phenomenon is associated with a benign tumor of the pituitary (adenoma) (47). Currently available treatment, consisting of surgery, radiotherapy, and medication with dopamine agonists or somatostatin analogues is not effective in all cases (48).
Pegvisomant (**8**, Figure 6), a competitive GH receptor antagonist, is a PEGylated form of B2036, a recombinant human GH antagonist (47). **8** contains nine mutated amino acids: eight at site 1, which increases its affinity for GH-binding protein (49 a,b), and one at site 2 (G120K), which prevents receptor dimerization and provides the basis for the antagonistic activity (47, 50). The pegylation of **8** offers a longer biological half-life (from approximatively 10 minutes to >70 hours) and reduces the renal clearance and immunogenicity (51, 52).

Antidotes

Radiogardase™ (Heyl Chemisch-Pharmazeutische Fabrik) (orphan drug)
Prussian blue (insoluble), 500 mg, capsule
Indication: ion exchange agent for treatment of patients with known or suspected internal contamination with radioactive cesium (Cs) and/or radioactive or non-active thallium (Th) to increase their rates of elimination.
Date approved: 02-10-2003

Cs -137 is widely used by industry and in medicine in a variety of devices and to treat certain cancers; non-radioactive Th in industry and as rat poison. The radioactive form of Th (Th-201) is used in small doses for medical imaging procedures. Contamination with Cs-137 or Th can occur through a variety of routes including ingestion, inhalation, or wounds and can cause serious illness or death when high radiation doses are absorbed and delivered to critical organs. At low doses such contamination has been associated with the development of cancer (53).
Insoluble prussian blue (**9**, Figure 7) exists in a face-centered cubic lattice structure with Fe(II), Fe(III) atoms occupying the corners of the cube, and the CN groups positioned on the sides (54). In the crystal lattice there are "holes" distributed randomly to more orderly, depending on the conditions in which the crystals are prepared (54, 55). The mechanism of uptake of Cs and Th is not fully understood, but these "holes" are believed to play an important role: a combination of chemical ion-exchange and physical adsorption is implicated (54, 56). Cs and Th that have been absorbed into the body are removed by the liver and passed into the intestine and are then re-absorbed through entero-hepatic circulation. **9** works by trapping Cs and Th in the intestine, so that they can be passed out of the body in the stool rather than be re-absorbed (57).

New Molecular Entities Approved in 2003 with Standard Review (see Figure 8)

Aloxi™ (MGI Pharma/Helsinn)
Palonosetron hydrochloride, 0.25 mg, injection
Indication: selective 5-HT_3 receptor antagonist for prevention of chemotherapy-induced nausea and vomiting.
Date Approved: 25-07-2003

Boniva™ (Roche/GlaxoSmithKline)
Ibandronate sodium, 2.5 mg, tablet
Indication: oral biphosphonate for the treatment and prevention of osteoporosis in women.
Date Approved: 16-05-2003
Cialis® (Lilly ICOS)
Tadalafil, 5, 10 & 20 mg, tablet
Indication: phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction in men.

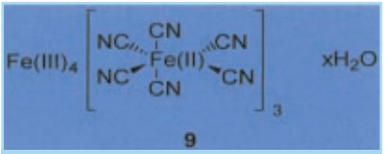
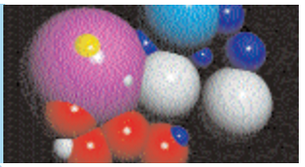


Figure 7 - Antidotes



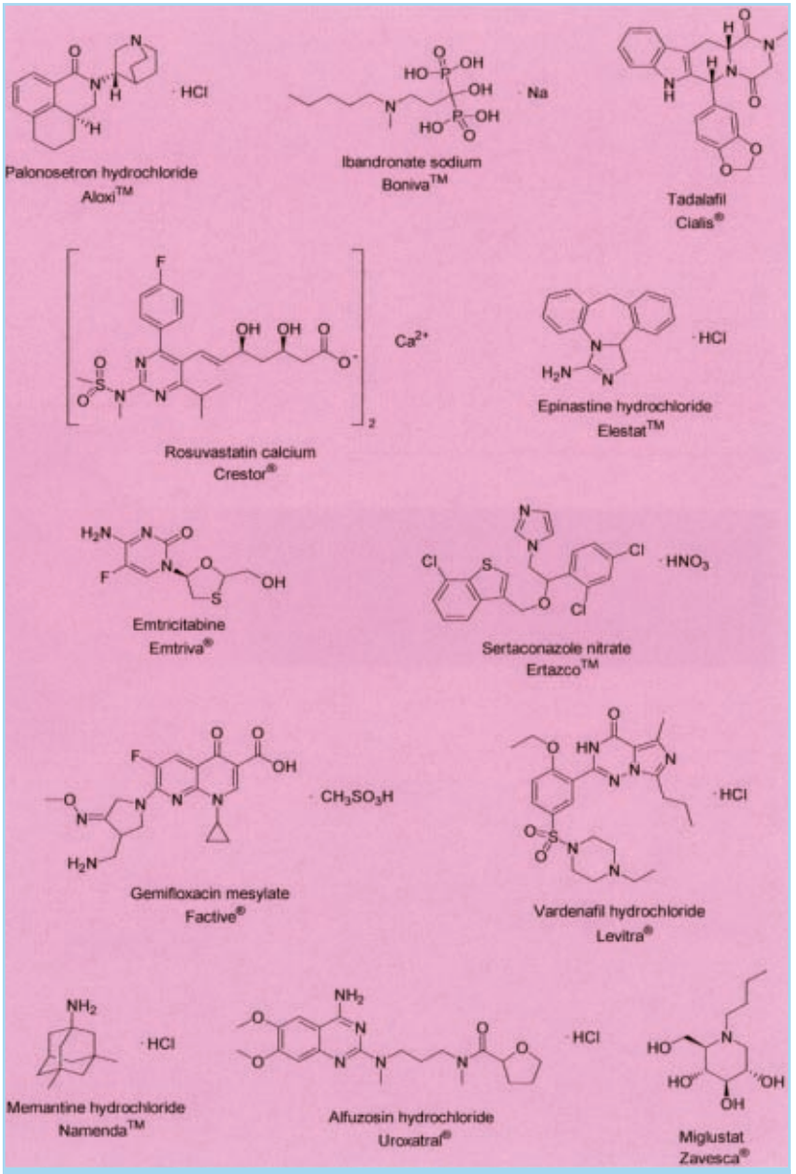


Figure 8 - Therapeutic classes of NME approved by "standard review

Date Approved: 21-11-2003 (available also in Italy (5))

Crestor® (AstraZeneca)
Rosuvastatin calcium, 5, 10, 20 & 40 mg, tablet
Indication: statin for use as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, non-HDL-C and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb); as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IIa and IIb); and to reduce LDL-C, total-C and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments or if such treatments are unavailable.
Date Approved: 12-08-2003 (available also in Italy (5))

Elestat™ (Allergan)
Epinastine hydrochloride, 0.05%, ophthalmic solution
Indication: topical antihistamine for the prevention of itching associated with allergic conjunctivitis.
Date Approved: 16-10-2003 (available also in Italy (5))

Emtriva® (formerly Coviracil, Gilead)
Emtricitabine, 200 mg, capsule
Indication: once-daily nucleoside reverse transcriptase inhibitor for use in combination with other anti-retroviral agents for the treatment of HIV-1 infection in adults.
Date Approved: 02-07-2003

Ertazco™ (Mylan/Ortho Neutrogena)
Sertaconazole nitrate 2%, cream
Indication: imidazole antifungal for topical treatment of interdigital tinea pedis in immunocompetent patients 12 years of age and older, caused by *Trichophyton rubrum, Trichophyton mentagrophytes and Epidermophyton floccosum*.
Date Approved: 12-10-2003

Factive® (LG Life Sciences/Oscient)
Gemifloxacin mesylate 320 mg, tablet
Indication: quinolone antibiotic for the treatment of community-acquired pneumonia and acute bacterial exacerbation of chronic bronchitis.
Date Approved: 04-04-2003

Levitra® (Bayer/GlaxoSmithKline)
Vardenafil hydrochloride, 2.5, 5, 10 & 20 mg, tablet
Indication: phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction in men.
Date Approved: 19-08-2003 (available also in Italy (5))

Namenda™ (Forest/Merz) (orphan drug)
Memantine hydrochloride, 5 & 10 mg, tablet
Indication: orally active NMDA antagonist for the treatment of moderate to severe dementia of the Alzheimer's type.
Date Approved: 16-10-2003

Uroxatral® (Sanofi-Synthelabo)
Alfuzosin hydrochloride, 10 mg, extended-release tablet
Indication: α_1-adrenergic receptor antagonist for the treatment of signs and symptoms of benign prostatic hyperplasia.
Date Approved: 12-06-2003

Zavesc® (formerly Vevesca) (Actelion) (orphan drug)
Miglustat, 100 mg, capsule

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