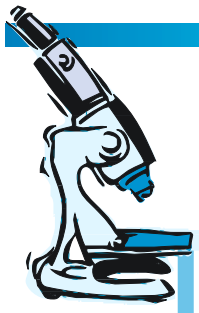

Osservatorio

Newly FDA-Approved Drugs (January-December 2001)

by Andrea Duranti

The aim of this review is to survey the new "Molecular Entities" (NME) approved by the Food and Drug Administration (FDA) in the year 2001 (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) (7 NME, 75 references) will be considered. As for the drugs subjected to "Standard Review" (i.e., those having similar therapeutic properties when compared to drugs already on the market) (17 NME), only basic information (product, sponsor, date approved, indication and structural formula) will be given [1]. This review follows the others about the NME approved by the FDA in 1998, in 1999, and in 2000 [2].

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 anti-HIV drugs are present as in 1998-2000 because of the great interest in the related diseases. In addition cardiovascular, as in 1998 and 1999, ophthalmic, as in 1999 and 2000, and antifungal drugs are reported in NME FDA-approved.

Antiviral drugs

Viread™ (Gilead Sciences)
Tenofovir disoproxil fumarate, 300 mg, tablet [3].
Indication: nucleotide analogue reverse transcriptase inhibitor for treatment of HIV infection when taken in combination with other antiretroviral agents; risk-benefit ratio in anti-retroviral-naive patients has yet to be determined.
Date approved: 26-10-2001 (accelerated approval)

Acquired immunodeficiency syndrome (AIDS) is caused by a retrovirus known as human immunodeficiency virus (HIV) (two types exist: HIV-1 and HIV-2, the latter of which is endemic to the populations of Africa). HIV enters the host cells by binding the receptor of CD4 lymphocytes, thus beginning a process of replication leading to a dramatic decrease in CD4 cells. Because a cure for HIV infection has not been found, the aim of current antiretroviral therapies is to block HIV replication for as long as possible. To this aim, and to reduce the resistance of the virus to a minimum, recommended therapies foresee the administration of multi-drug treatments (referred to as highly active antiretroviral therapy, HAART) employing several different Drugs, e.g., two nucleoside reverse transcriptase inhibitors (NRTIs) in association with a non-nucleoside reverse transcriptase inhibitor (NNRTIs) and/or a protease inhibitor (PI) [4]. Ideally, in order to inhibit the emergence of resistant variants, it is believed that at least two of the drugs should be changed in the course of therapy [5]; this hypothesis is supported by the identification of latent HIV in resting CD4 cells in patients treated with HAART [6]. However, since both NNRTIs and PIs suffer from class cross-resistance on therapeutic failure, NRTIs will remain essential components of HAART. In spite of this, the duration-dependent adverse effects that this class of compounds exhibit may limit their use [7]. The nucleotide class of reverse transcriptase inhibitors (NtRTIs), which offer improved potency by abbreviating intracellular activation pathway, can significantly improve the therapeutic options in HIV therapy [7].
Tenofovir disoproxil fumarate (**1**, Figure 2) is an adenosine phosphorylated derivative belonging to the NtRTIs, synthesized as described in [8]. **1** is active against retro- and hepadnavirus [9] and can be viewed as an acyclic nucleoside analogue that is extended by a phosphonate moiety, that is as a drug needing only two phosphorylation steps to be converted into the 5'-triphosphate active metabolite [10]; it is able to act as chain terminator at the substrate binding site of RT because its incorporation at the 3' end of the nascent DNA chain prevents further elongation [11]. **1** is a prodrug bearing labile lipophilic groups which permit its oral administra-

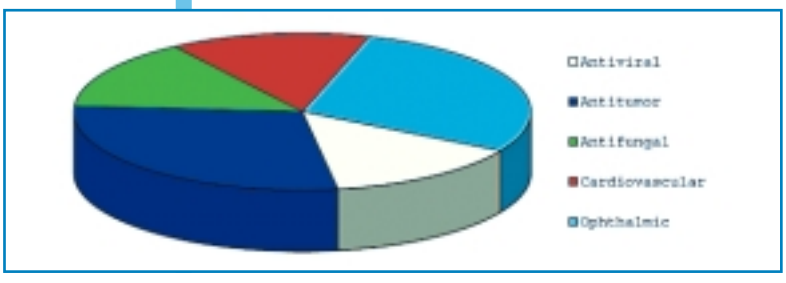

Figure 1 - Therapeutic classes of NME approved by "priority review"

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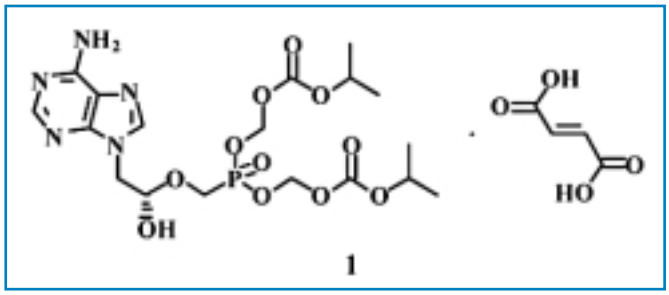

Figure 2

tion, thus facilitating the penetration of target cell membranes and enhancing bioavailability; on the contrary, in tenofovir (PMPA) this condition is slowed down since the negative charge of the phosphonate moiety significantly impairs cellular uptake. **1** exhibits a long intracellular half-life in both resting and activated peripheral blood mononuclear cells that permits once-daily administration [12]. **1** shows a favorable resistance profile against mutants resistant to various other RTIs, even after prolonged treatment for more than one or two years [13]. This is probably a result of the unique phosphonate bond of **1**, which also reduces the susceptibility of phosphorus to attack by pyrophosphate and ATP [14]. Interestingly, some novel amidate prodrugs of PMPA have been synthesized and tested to compare these new compounds with PMPA and ester prodrug **1** [15]. Finally, it is mentioned that the analysis of the results of trials with **1** conducted in treatment-naive subjects should be completed during the first half of 2002 [16]; moreover, because the approval of **1** was based on clinical trials involving patients who were previously treated with antiretrovirals, the risk-benefit ratio for untreated patients has yet to be determined [17].
An overview of the status of HIV pathology, new developments in anti-HIV chemotherapy, and strategies in the design of antiviral drugs are reported in [4, 11, and 13, respectively].

Antitumor drugs

Gleevec™ (formerly *Glivec*) (Novartis) (orphan drug)
Imatinib mesylate, 50 and 100 mg, capsule [18, 19].
Indication: protein-tyrosine kinase inhibitor for treatment of chronic myeloid leukemia in blast crisis or accelerated phase, or chronic phase after failure of interferon alfa therapy.
Date approved: 10-05-2001 (accelerated approval)

Chronic myeloid leukemia (CML) is a neoplastic affection deriving from two factors: mutation of bone marrow cells caused by the breakage of gene segments referred to as *abl* on chromosomes 9 and *bcr* on 22, and translocation of the *abl* protooncogene with fusion to the *bcr*, a recombination known as the Philadelphia chromosome [20]. This results in the production of an abnormal protein tyrosine kinase called *bcr-abl* [21], which determines uncontrollable proliferation and reduced apoptosis of white blood cells. CML develops in three phases: chronic, accelerated and blastic, which are differently characterized and progressively less lasting but more severe. Therefore, although radiation therapy, and the use of interferon-α with or without other drugs such cytarabine may lead to further improvements in the treatment of CML, and allogeneic stem cell transplantion (SCT) is the only real cure (but only 15-20% of CML patients are eligible for SCT due to the lack of

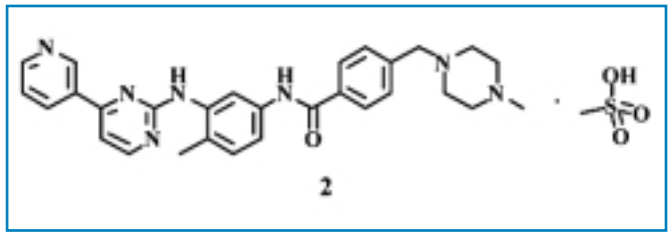

Figure 3a

suitable donors or age restrictions [18]), the most ideal treatment approach would be a specific inhibitor of the *bcr-abl*.
Imatinib mesylate (**2**, Figure 3a) is a 2-phenylaminopyrimidine derivative synthesized as described in [22]. **2** is a specific inhibitor of the translocation- created enzyme, its mechanism of action involving an interaction with ATP binding site in tyrosine kinase, that keeps *bcr-abl* in a non-active state in which Tyr^{393} in an activation loop is not phosphorylated [18, 23]. With **2**, for the first time it is possible to work with the necessary tools to probe the molecular anatomy of tumor cells in search of cancer-causing proteins [24]. As a result, it was observed that **2** very rapidly induces hematological remission in almost all chronic patients as well as major cytogenetic responses in about 50% of previously treated patients, and this figure may be nearer 80% in previously untreated patients. In addition, the drug's toxicity profile is generally acceptable for a drug used in the treatment of leukaemia [25].
On the contrary, there is no evidence that **2** will actually prolong survival: this is probable, but will not be known before one or two years [25]. Overviews about different approaches to initial treatment of the CML patient diagnosed in chronic phase and perspectives on the future of CML treatment are discussed in [26] and [26b], respectively. Finally, it should be mentioned that final results from Novartis' confirmatory study of **2** in newly diagnosed, previously untreated CML patients should be available in the fourth quarter of 2005 [27], and that several weeks ago the FDA approved **2** for the treatment of patients with metastatic and/or unresectable malignant gastrointestinal stromal tumors [28].

Zometa® (Novartis) (orphan drug)
Zoledronic acid disodium salt hydrate, 4 mg, injection [29, 30].
Indication: intravenous bisphosponate for treatment of hypercalcaemia of malignancy.
Date approved: 20-08-2001

Hypercalcaemia of malignancy (HCM) is a metabolic disease which commonly occurs in advanced cancer patients with and without evidence of skeletal involvement [31]. It results from increased calcium loss from bones and resorption with a subsequent rapid rise in serum calcium levels, caused by a disruption of the balance between osteoclasts (bone-resorbing cells) and osteoblasts (bone-forming cells) [30]. This situation is evident when humoral and paracrine factors secreted by the tumor cause an increase in the activity and proliferation of osteoclasts and inhibit activity of osteoblasts [30]. Biphosphonates (BPs) are a family of pyrophosphate analogs characterized by a phosphorus-carbon-phosphorus (P-C-P) backbone and are suitable for use in the treatment of a variety of metabolic bone diseases characterized by increased bone resorption [32]. Although the chemical characteristics of second generation compounds have lead to an improvement in antire-

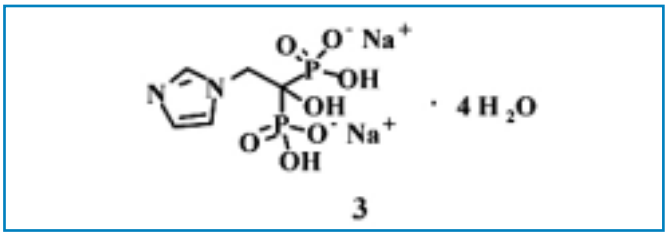

Figure 3b

sorptive potency and a decrease in infusion times of the drug, the need for new compounds has led to the development of a third generation of BPs.
Zoledronic acid (**3**, Figure 3b) is an imidazole derivative belonging to this generation, synthesized as described in [33]. Like other BPs, **3** acts through chelation of calcium ions by two phosphonate groups of P-C-P, which appear to be required for interaction with a molecular target in the osteoclast and for binding bone minerals [34, 35]. Studies of structure-activity relationships (SARs) conducted with BPs and **3** revealed that their antiresorptive potency is determined by the chemical and three-dimensional structure of the two side chains, attached to the central, geminal carbon atom [34, 36] and, in particular, by the basic nitrogen group [35a, 37]. An explanation of this behavior could be the discovery that the nitrogen-containing BPs (*N*-BPs) inhibit the biosynthetic mevalonate pathway, thereby preventing the post-translational prenylation of small GTP-binding proteins [38]. Very recently, it has been demonstrated that SARs of *N*-BPs for inhibition of bone resorption in vivo are related to differences in the ability to inhibit farnesyl diphosphate synthase rather than to differences in cellular uptake or bioavailability [34]. In comparison of pamidronate, a second-generation BP drug already present in the market, **3** shows a shortened infusion time (15 minutes vs. two to 12 hours) as well as improved efficacy [39] and a dramatically decreased risk of nephrotoxicity, related to the rate of infusion rather than the antiresorptive potency of drug [40]. A few weeks ago, the FDA approved a supplemental new drug application for **3** for "the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy" [41]. In addition, the FDA announced that approval of Zometa® 8 mg HCM retreatment dose, and develop of this drug for osteoporosis and for Paget's disease would need new studies [39].
Finally, it must be mentioned that another third-generation BP, namely ibandronate, is under investigation because of its antiresorptive potency [42].

Antifungal drugs

Cancidas® (Merck)
Caspofungin acetate, 50 and 70 mg, injection [43, 44].
Indication: glucan synthesis inhibitor for treatment of invasive aspergillosis in patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole.
Date approved: 26-01-2001

As a result of the growing population of immunocompromised patients, the incidence of fungal infections has increased sig-

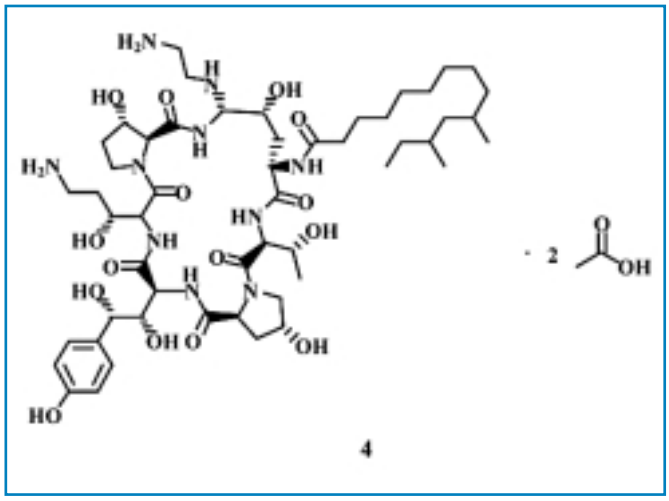

Figure 4

nificantly over the past twenty years [44]. Invasive aspergillosis is a term used to describe a group of fungal infections caused by members of the species *Aspergillus* which is the leading cause of pneumonic mortality in acute leukemia and in bone marrow/hematopoietic stem cell transplant recipients [45]. The chances of survival for people affected by these infections are tied to an early diagnosis, but unfortunately no good diagnostic tests are available; in addition, where this condition is possible, fungi are often refractory to treatment with the existing therapy [45]. The currently available therapies of first choice are amphotericin B, a fungicidal polyene also present as desoxycolate in a lipid formulation, or azoles (e.g. itraconazole), but administration of both leads to adverse effects: nephrotoxicity and cross-resistance, respectively; on the other hand, the target itself for activity, the fungal cell membrane, limits the opportunity to combine both classes or to employ them as reciprocal substitutes when a resistant organism is encountered [46]. Since the cell wall is a unique structure that permits selective targeting, fungicidals acting in this structure are attractive for clinical development.
Caspofungin acetate (**4**, Figure 4) is a semisynthetic derivative of pneumocandin B_0, synthesized as described in [47]. **4**, which belongs to a class of fungicidals referred to as the echinocandins, acts by interfering with cell-wall biosynthesis by non-competitive inhibition of 1,3-β-D-glucan synthesis, an enzyme system which is absent in mammalian cells but present in most pathogenic fungi [45, 48], and its effects appear to depend on fungal growth and metabolism [49]. **4** offers the advantages of a favorable tolerability profile, with no hepato- or nephrotoxicity, and a broad spectrum of activity. It, as well as other lipopeptide antifungal agents, has limited oral bioavailability: this fact has led to the development of compounds with the same mechanism of action of **4** but with the potential for oral absorption [50]. However, other inhibitory agents like **4**, that is FK463 or VER-002 and novel triazoles are under evaluation, whereas new lipid formulations of amphotericin B are licensed [51]. Phase IV studies of Cancidas® are in progress [52].

Cardiovascular drugs

Arixtra® (Sanofi-Synthelabo and Organon)
Fondaparinux sodium, 2.5 mg, prefilled syringe.

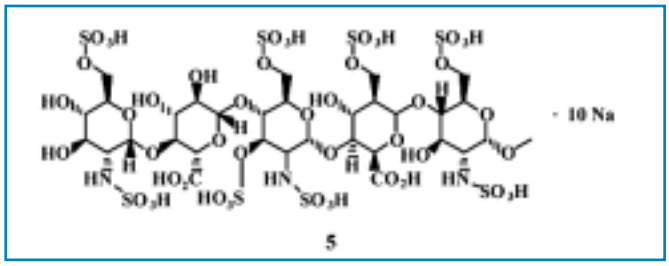

Figure 5

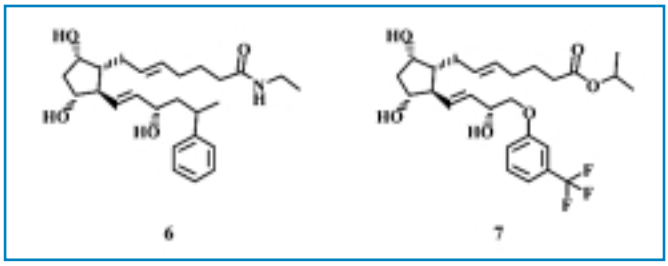

Figure 6

Indication: synthetic pentasaccharide for prevention of deep vein thrombosis which may lead to pulmonary embolism in patients undergoing hip fracture surgery, hip replacement surgery or knee replacement surgery.
Date approved: 07-12-2001

Deep vein thrombosis (DVT) is a blood clot (thrombus), which can affect both surgical and medical patients and cause significant rates of early death via pulmonary embolism (PE) [53] as a consequence of a complex cascade of reactions caused by the coagulation system. Factor Xa, which belongs to the family of trypsin-like serine proteases, is fully involved in this situation because both intrinsic and extrinsic pathways converge toward it; therefore, it amplifies the coagulation cascade by producing many thrombin molecules, which ultimately transform fibrinogen to the fibrin clot [54]. However, both DVT and PE may be asymptomatic and difficult to detect; thus, physicians focus on preventing their development by using mechanical [55] or drug therapies [56]. Current prophylactic drug treatments comprise heparins, including low-molecular-weight heparins (LMWH), and oral vitamin K antagonists such as warfarin. The selectivity of LMWH for factor Xa over thrombin, along with some disadvantages produced by the classes of compounds mentioned above, has prompted interest in the discovery and development of selective Xa inhibitors [53, 57].
Fondaparinux sodium (**5**, Figure 5), synthesized as described in [58], represents the first synthetic anticoagulant. **5** consists of five saccharide units with sulfate groups strategically positioned to bind strongly and exclusively to antithrombin (AT), the primary endogenous regulator of blood coagulation [59]. **5** induces a conformational change in the AT molecule, thus strongly potentiating the natural neutralization of factor Xa by AT [60]: each molecule of **5** binds to one molecule of AT but is then released, allowing it to consecutively bind to several AT molecules [54, 59c]. The AT conformation change is permanent once the covalent complex with factor Xa is formed, and the enzyme-inhibitor complex is then cleared from circulation [54, 59a,c, 60, 61]. **5** has a linear, dose-dependent pharmacokinetic profile, which provides a highly predictable response [54]; it is 100% bioavailable, has a rapid onset of action, and has a half-life of 14 to 16 hours, allowing sustained antithrombotic activity over a 24-hour period [54]. **5** does not affect prothrombin time or activated partial thromboplastin time, nor does it affect platelet function or aggregation, and does not determine heparin-induced thrombocytopenia [54]. In comparative studies conducted with enoxaparin, a LMWH in use for the prevention of thromboembolism after hip fracture surgery and after elective major knee surgery, **5** was more effective [62]. In summary, **5** appears to meet the criteria for an ideal antithrombotic agent, but it is not to be used in patients with severely impaired kidney function or who weigh less than fifty kilograms, because of the increased risk for serious bleeding [63].

Ophthalmic drugs

Lumigan® (Allergan)
Bimatoprost, 0.03%, ophthalmic solution [64].
Indication: prostamide for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.
Date approved: 16-03-2001

Travatan™ (Alcon)
Travoprost, 0.004%, ophthalmic solution [65].
Indication: prostaglandin analog for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.
Date approved: 16-03-2001

Open-angle glaucoma (OAG) is the most common type of glaucoma, which may be defined as a progressive optic neuropathy with characteristic changes in the optic nerve head and the visual field. In OAG the fluid that normally flows through the pupil into the anterior chamber cannot get through the trabecular meshwork (the eye's filtration area) to the normal drainage canals [66]. This condition is characterized by an elevated intraocular pressure (IOP), which is normally maintained by the balance between inflow and outflow of aqueous humor in the eye, but in the presence of OAG is elevated as the result of an impaired outflow, and constitutes an important risk factor. Both surgical and medical treatment can be aimed at inflow as well as outflow [67]. The non-selective β-adrenergic antagonists, such as timolol, are still the most commonly prescribed agents for glaucoma management; however, various side effects, such as cardiac and pulmonary disease, have led to the development of new classes of ocular hypotensive Drugs, like prostaglandin (PG) analogues.
Bimatoprost (**6**) and travoprost (**7**) (Figure 6) are two PG analogues, based on $PGF_{2\alpha}$, which are synthesized as described in [64] and [65], respectively. **6** appears to mimic the activity of a newly discovered family of fatty acid amides (FAAs), called the prostamides, biosynthesized from a FAA called anandamide by cyclooxygenase-2 (COX-2) [68], mutations of which have been reported in IOP [69]. The primary hypotension action of **6** is due to a reduction in tonographic resistance to outflow, enhancing the pressure-sensitive outflow pathway; additional effects include a lowering of the extraocular recipient pressure and an increase in the rate of flow via the pres-

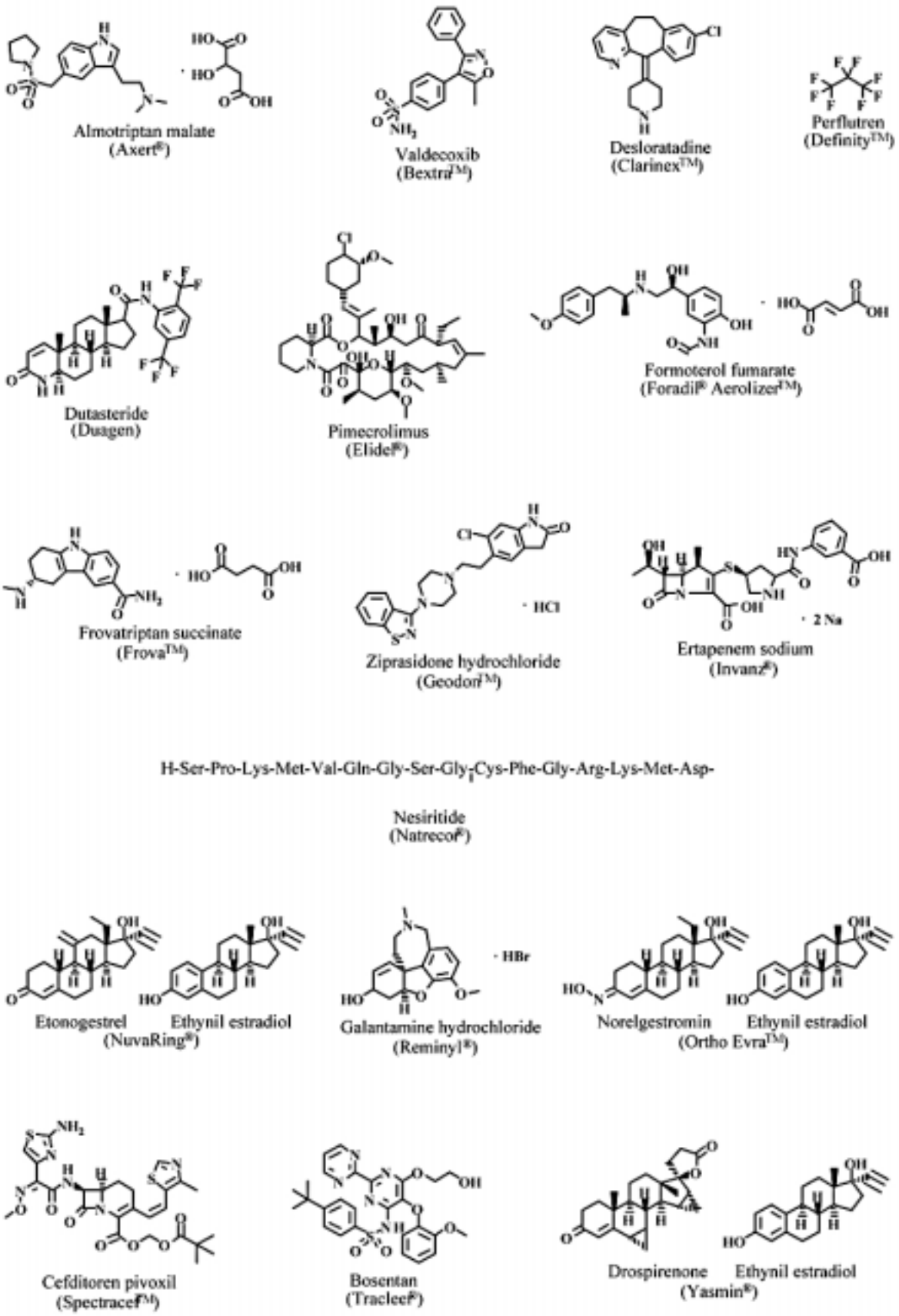
Almotriptan malate
(Axert®)
Valdecoxib
(Bextra™)
Desloratadine
(Clarinex™)
Perflutren
(Definity™)
Dutasteride
(Duagen)
Pimecrolimus
(Elidel®)
Formoterol fumarate
(Foradil® Aerolizer™)
Frovatriptan succinate
(Frova™)
Ziprasidone hydrochloride
(Geodon™)
Ertapenem sodium
(Invanz®)
H-Ser-Pro-Lys-Met-Val-Gln-Gly-Ser-Gly-Cys-Phe-Gly-Arg-Lys-Met-Asp-
Nesiritide
(Natrecor®)
Etonogestrel
Ethynil estradiol
(NuvaRing®)
Galantamine hydrochloride
(Reminyl®)
Norelgestromin
Ethynil estradiol
(Ortho Evra™)
Cefditoren pivoxil
(Spectracef™)
Bosentan
(Tracleer®)
Drospirenone
Ethynil estradiol
(Yasmin®)

Figure 7

sure-insensitive outflow pathway [70], which is the primary mechanism of action of **7** [71], as well as of latanoprost and isopropyl unoprostone, other PG analogues marketed in the US since 1996 as Xalatan® [72] and since 2000 as Rescula® [2d], respectively. **7** is a prodrug that is rapidly hydrolyzed by esterase in the cornea to the biologically active free acid, unlike **6** [73]. **6** and **7** received the second-line indication because a significant improvement over timolol in lowering intraocular pressure was demonstrated statistically, not clinically [74, 75].

New molecular entities approved in 2001 with standard review (Figure 7)

Axert® (Pharmacia)
Almotriptan malate, 6.25 and 12.5 mg, tablet.
Indication: 5-$HT_{1B/1D}$ receptor antagonist for acute treatment of migraine with or without aura in adults.
Date approved: 07-05-2001 (available also in Italy)

Bextra™ (Searle)
Valdecoxib 10 and 20 mg, tablet.
Indication: COX-2 inhibitor for treatment of primary dysmenorrhea and adult osteoarthritis and rheumatoid arthritis.
Date approved: 16-11-2001

Clarinex™ (Schering-Plough)
Desloratadine, 5 mg, tablet.
Indication: metabolite of the non-sedating antihistamine loratidine (*Claritin*®) for the relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis in patients 12 years and older.
Date approved: 21-12-2001

Definity™ [Bristol-Myers Squibb Medical Imaging (formerly DuPont Pharmaceuticals; agent licensed from ImaRx)]
Perflutren, injection.
Indication: lipid microsphere formulated ultrasound contrast agent for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve delineation of the left ventricular endocardial border.
Date approved: 31-07-2001

Duagen (GlaxoSmithKline)
Dutasteride, 0.5 mg, soft-gelatine capsule.
Indication: 5α-reductase inhibitor for treatment of signs and symptoms of benign prostatic hyperplasia.
Date approved: 20-11-2001

Elidel® (Novartis)
Pimecrolimus, 1%, cream.
Indication: ascomycin macrolactam derivative for short-term and intermittent long-term therapy in the treatment of mild to moderate atopic dermatitis in non-immunocompromised patients two and older, in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are intolerant of or not adequately responsive to alternative, conventional therapies.
Date approved: 13-12-2001

Foradil® *Aerolizer*™ (Novartis Pharmaceuticals)
Formoterol fumarate, 12 mcg, inhalation powder.
Indication: selective β_2-agonist for maintenance treatment of asthma, for prevention of bronchospasm in adults and children five years and older with reversible obstructive airways disease (including patients with symptoms of nocturnal asthma who require regular treatment with inhaled, short-acting β_2-agonists) and for acute prevention of exercise-induced bronchospasm in adults and children twelve years and older.
Date approved: 16-02-2001 (available also in Italy)

Frova™ (formerly *Frovelan* and *Miguard*) (Élan)
Frovatriptan succinate, 2.5 mg, tablet.
Indication: 5-$HT_{1B/1D}$ agonist for acute treatment of migraine.
Date approved: 08-11-2001

Geodon™ (formerly *Zeldox*) (Pfizer)
Ziprasidone hydrochloride, 20, 40, 60 & 80 mg, capsule.
Indication: antipsychotic for treatment of schizophrenia.
Date approved: 05-02-2001

Invanz® (Merck)
Ertapenem sodium, 1 g, injection.
Indication: injectable antibiotic for treatment of complicated intra-abdominal infections, complicated skin and skin structure infections, community-acquired pneumonia, complicated urinary tract infections, including pyelonephritis, and acute pelvic infections, including postpartum endomyometritis, septic abortion and post-surgical gynecologic infections.
Date approved: 21-11-2001

Natrecor® (Scios)
Nesiritide, 1.5 mg, injection.
Indication: recombinant human B-type natriuretic peptide for intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity.
Date approved: 10-08-2001

NuvaRing® (Organon)
Etonogestrel, 0.12 mg, and ethinyl estradiol, 0.015 mg, vaginal ring.
Indication: contraceptive ring.
Date approved: 03-10-2001

Ortho Evra™ [Ortho-McNeil (Johnson & Johnson's company)]
Ethinyl estradiol, 0.75 mg, and norelgestromin, 600 mg, transdermal system.
Indication: seven-day contraceptive patch.
Date approved: 20-11-2001

Reminyl® (Janssen, Shire co-developed)
Galantamine hydrobromide, 4, 8 & 12 mg, tablet.
Indication: reversible cholinesterase inhibitor for treatment of mild to moderate dementia of the Alzheimer's type.
Date approved: 28-02-2001 (available also in Italy)

Spectracef™ (TAP)
Cefditoren pivoxil, 200 mg, tablet.
Indication: cephalosporin antibiotic for treatment of acute exacerbation of chronic bronchitis caused by *H. influenzae*, *H. parainfluenzae*, *S. pneumoniae* or *M. catarrhalis*; pharyngitis/tonsillitis caused by *S. pyogenes*; and uncomplicated skin and skin structure infections caused by *S. aureus* or *S. pyogenes*.
Date approved: 29-08-2001

Tracleer® (Actelion)
Bosentan, 62.5 and 125 mg, film-coated tablet.
Indication: dual endothelin receptor antagonist for treatment of pulmonary arterial hypertension.
Date approved: 20-11-2001

Yasmin® (Berlex)
Drospirenone, 3 mg, and ethinyl estradiol, 0.030 mg, tablet.
Indication: contraceptive.
Date approved: 11-05-2001

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