di Andrea Duranti

Newly FDA-Approved Drugs (January-December 2002)

The aim of this review is to survey the new "Molecular Entities" (NME) approved by the Food and Drug Administration (FDA) in the year 2002 (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, 60 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) (10 NME), only basic information (product, sponsor, date approved, indication, structural formula and availability in Italy) will be given [1]. This review follows the others about the NME approved by the FDA in the years 1998-2001 [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 antiviral drugs are present (as in 1998-2001) as are cardiovascular drugs (as in 1998, 1999 and 2001) because of the great interest in the related diseases. In addition antimicrobial, IBS, and anticataplexic drugs and enzymatic inhibitors are reported in FDA-approved NME.

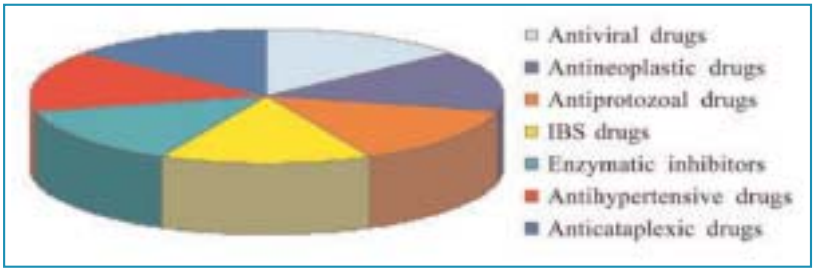

Figure 1 - Therapeutic classes of NME approved by "priority review"

Antiviral drugs

Hepsera® (Gilead Sciences)
Adefovir dipivoxil, 10 mg, tablet [3]
Indication: treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases or histologically active disease.
Date approved: 20-09-2002

Hepatitis B virus (HBV) is a hepadnavirus, one of the family of viruses characterized by a circular, partially double-stranded, partially single-stranded DNA genome [4]. After entering the hepatocyte, viral plus strand DNA synthesis is completed and joins the minus strand DNA to form covalently closed circular DNA (cccDNA) in the nucleus [5]. The cccDNA plays a key role in the maintenance of chronic HBV infection as it serves as a template for transcription to RNA, then reverse transcription to DNA and translation for proteins to form new viruses to infect new hepatocytes and so on [5]. Essentially, HBV is not itself cytopathic. Instead, chronic HBV is a dynamic state of interaction among HBV, hepatocytes and the immune system of the host [5] (a detailed description of life cycle, viral dynamics and kinetics of HBV is in [4, 6]). The long-term consequences of chronic HBV include cirrhosis, end-stage liver disease, and hepatocellular carcinoma [7]. This is a serious problem in most cases because spontaneous remission in chronic HBV is not frequent [3a]; in addition, only a minority of patients respond to therapy with current interferon-α treatments, the use of which is limited by various side effects, or lamivudine, the efficacy of which is compromised by the development of viral resistance to drugs, six-nine months after starting therapy [3a, 4-7]. Studies about the hypothesized mechanism of resistance are reported in [8] and [4]. The nucleotide class of reverse transcriptase inhibitors (NtRTIs), which offer improved potency by abbreviating intracellular activation pathway, can significantly improve the therapeutic options in chronic HBV therapy [9]. Adefovir dipivoxil (**1**, figure 2), a phosphorylated adenosine derivative belonging to the NtRTIs, is synthesized as described in [10]. **1** is a bis ester prodrug bearing labile lipophilic groups that permit oral administration, and a conversion to adefovir (PMEA) in the gastrointestinal tract and transport of this product into cells [3a], a situation slowed down for PMEA since the negative charge of the phosphonate moiety significantly impairs cellular uptake. **1** is active against herpes, retro- and hepadnavirus [3a] and can be viewed as an acyclic nucleoside analogue that is extended by a phosphonate moiety [11].

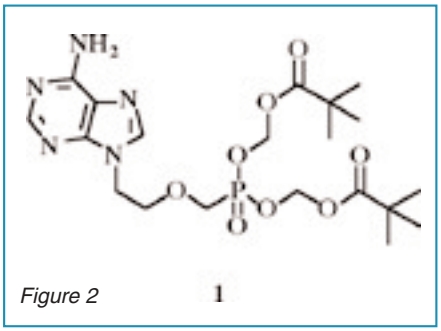

Figure 2 **1**

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1 inhibits HBV polymerase by direct binding in competition with endogenous substrate [deoxyadenosine triphosphate (dATP)] and, after incorporation into viral DNA, results in the chain termination of DNA synthesis [1a]. **1** has a long intracellular half-life that permits once-daily administration [12] and exhibits no cross-resistance with lamivudine and is effective against lamivudine-resistant HBV [4, 13]. Lack of cross-resistance is thought to be a result of the predicted stereochemically feasible binding of PMEA diphosphate, which contains a flexible acyclic linker in place of the unnatural l-nucleoside ring of lamivudine, at the active sites of both wild-type and YMDD-mutant HBV polymerase models [4, 8a]. The hypothesis about lack of HBV resistance to **1** is based on the fact that in PMEA diphosphate, on the contrary to the case of lamivudine, the deoxyribose of the dATP is replaced by a minimal acyclic structure whose flexibility allows PMEA to adjust to the structure of the viral polymerase and adopt a conformation that avoids steric hindrance with mutated amino acid side chains [4, 8a]; in addition, the fact that only two phosphorylation steps to convert **1** into the 5'-triphosphate active metabolite are needed, may lead to a potent and durable inhibition of HBV replication that decreases replication space and generation of potentially resistant mutants [4].

Antineoplastic drugs

Eloxatin™ (Sanofi-Synthelabo)
Oxaliplatin, 50 & 100 mg, injection [14]
Indication: in combination with infusional 5-fluorouracil/leucovorin (5-FU/LV) for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within six months of completion of first-line therapy with the combination of bolus 5-FU/LV and irinotecan (Pharmacia's *Camptosar*®).
Date approved: 09-08-2002 (also available in Italy [15])

One million patients worldwide are diagnosed with colorectal cancer each year, and the disease is a major cause of cancer mortality in developed countries [14a]. Surgery for localized disease can prolong survival, but approximately 50% of patients present or develop metastases and surgery is possible in ≤10% of these patients [14a], when metastatic disease is confined to the liver and potentially resectable after chemotherapy [16]. Once colorectal cancer has metastasized, the average survival duration without chemotherapy is around 3-9 months [16]. To improve survival and quality of life of the majority of patients the only option is therefore palliative chemotherapy, which has relied over the last four decades on the intravenous administration of 5-FU and 5-FU/folinic acid regimens [14a]. However, in metastatic setting, this therapy has been plagued by poor response rate (~20%) and not long median survival (~1 year) [17]. The introduction of thymidylate synthase modulators such as levamisole and LV has improved response rates, but progression-free survival and overall survival have remained unaffected [17]. Manipulation of the 5-FU protocol, such as infusional instead of bolus administration, yielded marginal improvements [17]. Current strategies, comprising these drugs and others introduced in the last five years [16-18], involve combination therapies because this approach is the most effective [17]. Oxaliplatin (**2**, Figure 3), a complex in which the platinum atom is linked with 1,2-diaminocyclohexane (DACH) and an oxalate ligand as a leaving group [19], is synthesized as described in [20]. **2** undergoes nonenzymatic conversion of the labile oxalate portion to several transient reactive species that covalently bind with macromolecules in physiological solutions [14b]. This type of binding produces both inter- and intrastrand Pt-DNA crosslinks with the *N*-7 position on guanine residues that result in the inhibition of DNA replication and transcription, a cell-cycle nonspecific process [14b, 21]. **2**, however, is a "third generation" platinum analogue different from other complexes in that this metal forms a bulkier product because of the presence of the DACH moiety [14b]; this results in molecular distortion that differs from that seen with non-DACH platinum agents, and is thought to lead to enhanced cytotoxicity, circumvention of cross-resistance, and clinically significant differences in terms of recognition by proteins [14b, 14c]. Finally, an approval for a new indication for first-line use of the colorectal cancer therapy is expected in december of this year [22]; in addition, Sanofi-Synthelabo will submit survival data on Eloxatin™ by second quarter of 2004 [23].

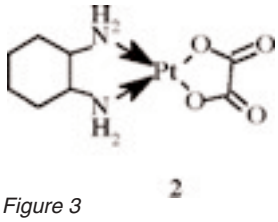


Figure 3

Antiprotozoal drugs

Alinia™(Romark)
Nitazoxanide, 100 mg/5 mL, oral suspension
Indication: antiprotozoal agent for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in pediatric patients one to eleven years old.
Date approved: 22-11-2002

Infectious diarrhea (ID) is an alteration of normal bowel habits caused by infectious bacteria, viruses or protozoa (including *Cryptosporidium parvum* and *Giardia lamblia*) normally contracted by ingestion of contamined water or food [24]. Most cases of ID are self-limiting in nature, resolving spontaneously after a few days. Acute cases of ID can, however, lead to dehydration and even death. Persistent or chronic diarrhea often associated with intestinal protozoan infections can also cause serious long-term consequences, including malnutrition and impairment of physical or cognitive development [24]. The risk of contracting ID diseases can be reduced by improved sanitary conditions, but they are very difficult to prevent [24]. Specific diagnosis of the cause of the ID, however, requires the collection of fecal samples for microscopic examination or cultures to grow bacteria. The time required to conduct these fecal tests can delay treatment of the patient for several days, and the accuracy of the tests is not optimal. As a result, many physicians view fecal tests as an unnecessary expense and inconvenience, particularly if they believe the infection will ultimately be resolved spontaneously [24]. The first step in treating diarrhea of any origin is to initiate rehydration therapy, orally or intravenously if necessary. Then, a diagnosis of the causative organism should be made and, where appropriate, antimicrobial agents should be administered to reduce the duration of diarrhea and prevent potential long-term consequences of the infection [24]. Metronidazole, although not approved for use by the FDA, has been the treatment of choice

for giardiasis [25], probably the most common pathogenic parasitic infection disease in humans [26]. Paromycin and azythromycin have been used for cryptosporidiosis, but neither has been clearly demonstrated to be effective against this pathology, which remain problematic above all in immunosuppressed patients not having access to highly active antiretroviral therapy (HAART) [27].
Nitazoxanide (**3**, Figure 4) is a nitrothiazolyl salicylamide derivative synthesized as described in [28]. **3** is the first drug approved by FDA for treatment of cryptosporidiosis and the first to become available as a liquid for treatment of giardiasis [25].

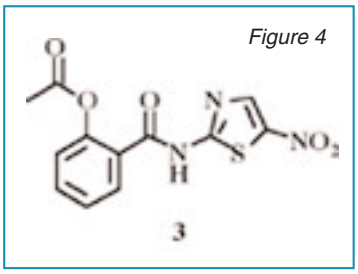


Figure 4

The exact mechanism of action of **3** is unknown but is thought to be related to inhibition of the pyruvate: ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reactions, essential to anaerobic energy metabolism [25], in analogy with what has been demonstrated in other microorganisms [29]. In contrast with nitroimidazoles, **3** appears to interact directly with PFOR (i.e., **3** is not dependent on reduced ferredoxin), and the products of **3** activation do not induce mutation in DNA [29]. This distinct behaviour is important in explaining the therapeutic efficacy of **3** against organisms displaying a high level of resistance to metronidazole [29]. The DNA-derived PFOR protein sequence of *C. parvum* appear to be similar to that of *G. lamblia* [30]. At present, in view of the distinct mechanism of **3** action, this drug might also be a good candidate for use in multidrug therapy, which is now generally advocated for treating parasitic infections in community-based programmes and for reducing the possible emergence of resistance [29]. A brief description of clinical studies about cryptosporidiosis and giardiasis is given in [25]. Finally, Romark expects approval in the first half of 2004 for a tablet formulation of Alinia™ for use in immunocompetent adults and adolescents with diarrhea associated with *G. lamblia* and *C. parvum* [31].

IBS drugs

Zelnorm® (formerly *Zelmac*) (Novartis)
Tegaserod maleate, 2 & 6 mg, tablet [32]
Indication: 5-HT_4 partial agonist for short-term treatment of women with constipation-predominant irritable bowel syndrome.
Date approved: 24-07-2002

Irritable bowel syndrome (IBS) is a functional bowel disorder in which abdominal discomfort or pain (the key symptom that must be present to make a diagnosis) is associated with altered bowel habits (diarrhea, constipation or alternating diarrhea and constipation), and with features of altered defecation according to Manning, Rome I and Rome II criteria [32a, 33]. IBS comprises a combination of recurring gastrointestinal symptoms that are not associated with structural or biochemical causes [32a]. It is considered a biopsychosocial disorder resulting from a combination of three interacting mechanisms: psychosocial factors, altered motility and transit which reflect severity of bowel dysfunction and increased sensitivity of the intestine or colon [34]. Recent research demonstrates that serotonin (5-hydroxytryptamine, 5-HT) is directly involved in initiating the peristaltic reflex and facilitates intraluminal secretions [32a, 35]. In addition, this research has focused on the possibility of altered autonomic integration of the serotoninergic and adrenergic systems in patients with IBS [32a, 35]. While these systems are normally balanced, it was recently postulated that IBS with constipation may be associated with an adrenergic predominance and subsequent reduction in serotoninergic influence [32a, 35]. The resulting increase in inhibitory dopaminergic activity and subsequent reduction in the bioavailability of acetylcholine would lead to reduced contractility of the gastrointestinal tract [32a, 35]. As a result, treatment of IBS should be based on the nature and severity of the symptoms (diarrhea, constipation or pain), the degree of physiological disturbance and functional impairment [33a], and pharmacological treatments recommended for patients with moderate to severe symptoms. An overview on IBS management is shown in [36]. At the present, fibers and bulking agents are commonly prescribed for IBS. However, clinical trials support only limited benefit for constipation and not for other symptoms [37]. Meta-analyses have concluded that there is insufficient evidence to support a benefit over placebos [37]. Cisapride, a mixed 5-HT_4 agonist/5-HT_3 partial antagonist drug, is known to accelerate gastric emptying and to enhance gastric accomodation, but it has been withdrawn from use because of rare cardiac toxicity [37a].

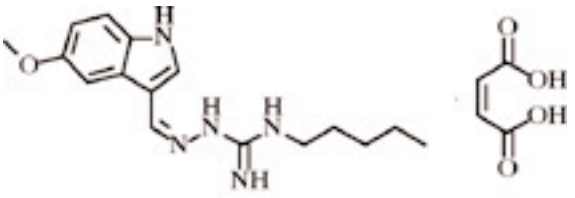


Figure 5 **4**

Tegaserod maleate (**4**, Figure 5) is an aminoguanidine indole derivative, structurally similar to 5-HT, synthesized as described in [38]. **4** is the first selective 5-HT_4 receptor partial agonist to be approved for IBS-C syndrome [32a]. **4** stimulates the peristaltic reflex, resulting in acceleration of intestinal and colon transit [39], because, when the lumen of the gut is distended in response to a meal, 5-HT is released [35]. This initiates a cascade of events that involves both excitatory and inhibitory interneurons and results in peristalsis [35]. The motivations behind the design of **4** were based on three observations of the pharmacokinetics and pharmacodynamics of the older benzamide prokinetics, such as cisapride. These achieved their effect through nonselective binding, producing non specific and at times unwanted adverse effects. Secondly, dosing up to four times a day to achieve a desired therapeutic outcome was troublesome for patient compliance. Lastly, any 5-HT_4 receptor agonist will need to be gut-specific and should be designed so as not to cross the blood-brain barrier [40]. **4** is the product of the medicinal chemistry program addressing these three issues: it is a specific 5-HT_4 receptor agonist, it achieves its therapeutic goal with a reduced dosing schedule, and it is devoid of significant CNS side effects [40]. Potential future therapies for IBS-C are summarized in [37a].

Enzymatic inhibitors

Orfadin® (Swedish Orphan) (orphan drug)
Nitisinone, 2, 5 & 10 mg, capsule
Indication: 4-hydroxyphenylpyruvate dioxygenase inhibitor, adjunctive therapy to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT1).
Date approved: 18-01-2002

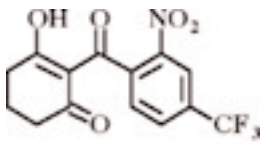


Figure 6 5

HT1 is a human disease caused by a deficiency of enzyme fumarylacetoacetate hydrolase (FAH), leading to accumulation of tyrosine metabolites that result in liver and kidney damage [41]. This disorder has importance as a model of spontaneous self-correction of liver disease, and of liver repopulation by transplanted cells and in gene therapy, and as a genetic cause of hepatocarcinoma [42]. The "classic" treatment of HT1 consists of dietary restriction of phenylalanine and tyrosine, but this regimen does not prevent progression of the disease [42]. In addition, the beneficial effects of liver transplantation suggest that expression of a normal cDNA in hepatocytes would alleviate the defect; therefore, HT1 is a candidate disorder for gene therapy directed at the liver [42].
Nitisinone (**5**, Figure 6), a 2-benzoylcyclohexane-1,3-dione (triketone) herbicide synthesized as described in [43], is the first drug approved for HT1. **5** acts by competitively inhibiting 4-hydrophenylpyruvate dioxygenase (HPPD), an enzyme upstream of FAH in the tyrosine metabolic pathway [44, 45]. Structure-activity relationship studies revealed that, for a potent HPPD inhibitor, a 2-benzoylethen-1-ol substructure is the minimum substructure required [46], and the presence of a strongly electronegative group at the ortho position and the conformation of the benzene ring moiety are crucial [47]. Recently, it was suggested that the *ortho*-positioned nitro group of **5** can directly interact with the active site of the enzyme through a keto-enol form making a terdentate coordination, stronger than that bidentate of 4-HPP, the natural substrate of HPPD [48], and this form and a coplanar stucture are absolutely necessary in order to chelate with the enzyme-bound ferric iron [49], as previously hypothesized in [50]. In conclusion, in those patients who do not respond to **5** therapy or show evidence of hepatic malignancy, orthotopic liver transplantation remains the treatment of choice [42]. An application for the use of **5** in alkaptonuria, a pathology involving homogentisate 1,2-dioxygenase, another enzyme of tyrosine metabolism, was filed in 2001 [51].

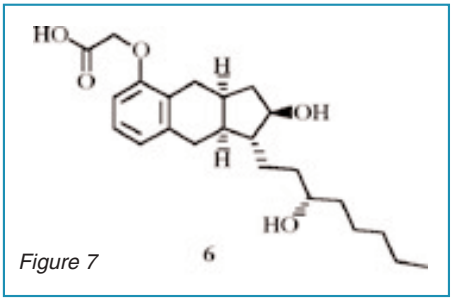


Figure 7 6

Antihypertensive, vasodilator drugs

Remodulin™ (United Therapeutics) (orphan drug)
Treprostinil sodium, 1, 2.5, 5 & 10 mg/mL, injection [52]
Indication: synthetic prostacyclin analog for treatment of pulmonary arterial hypertension in patients with NYHA (New York Heart Association) class II-IV symptoms to diminish symptoms associated with exercise.
Date approved: 21-05-2002 (accelerated approval)

Pulmonary arterial hypertension (PAH) is characterized by increased above normal blood pressure within the pulmonary arterial system [52]. This causes injury to the endothelial cells lining lung capillaries, thus affecting their interaction with nearby smooth muscle cells, which contract more than normal, thus narrowing the vessels and increasing resistance to blood flow [52]. This increase in resistance in turn places stress on the right ventricle and failure of this ventricle may develop due to the required increase in work [52]. PAH is a heterogeneous condition with a wide range of causes, generally considered a rare and rapid lethal condition with poor prognosis and few or no treatment options [53]. Medical therapies include anticoagulants, diuretics, calcium blockers and endothelin receptor antagonists with the aim of reducing or facilitating the work of the right ventricle, but all the drugs included in these classes can present adverse effects [52-54]. In addition, epoprostenol (prostacyclin), although apparently an ideal solution affecting both the pulmonary and systemic circulations, has an extremely short half-life (3-6 min) and is degraded by the gastrointestinal tract [52, 55]. This makes infusion via catheter implanted in the neck indispensable with delivery controlled by a portable pump and protection of the drug from light during reconstitution and infusion [52].
Treprostinil sodium (**6**, Figure 7) is a benzindene analog of prostacyclin synthesized as described in [56]. **6** causes vascular smooth muscle relaxation by binding to a membrane-associated, G-protein-coupled receptor, activating adenylate cyclase and production of cyclic adenosine monophosphate (cAMP) [54]. **6** has a half-life of 3 hours, is stable at room temperature [55] and is administered by subcutaneous infusion, which permits the elimination of the risk of sepsis infection, hospitalization associated with catheters and other several advantages [52, 55]. For these reasons, **6** is more convenient and less invasive than epoprostenol, but less convenient than bosentan, an endothelin receptor antagonist, which can be taken orally, but is hepatotoxic in some patients [54].

Anticataplexic drugs

Xyrem® (Orphan Medical) (orphan drug)
Sodium oxybate, oral solution
Indication: gamma hydroxybutyrate for the treatment of cataplexy associated with narcolepsy.
Date approved: 17-07-2002

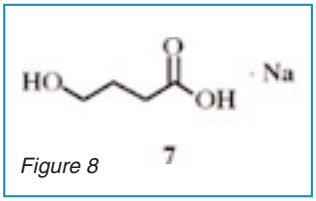


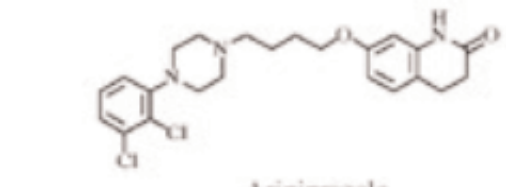
Figure 8 7

Narcolepsy is a lifelong neurological disorder characterized by fragmentation of nighttime sleep, daytime somnolence, cataplexy, sleep paralysis and hypnagogic allucination [57]. The symptoms of the latter three diseases are related to abnormal regulation of rapid

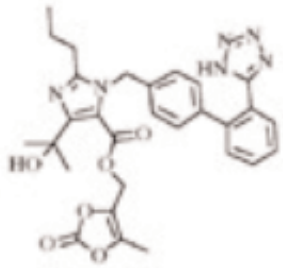
eye movement (REM) sleep [57]. Cataplexy is characterized by the sudden partial or total loss of muscle control in response to extreme emotional stimuli such as laughter, anger, or surprise [58]. The symptoms of cataplexy are typically treated with tricyclic antidepressants or selective serotonin reuptake inhibitors, but tolerance to their effects can occur and rebound cataplexy is possible if they are discontinued abruptly [57b]. In addition, these conventional treatments do not restore the integrity of sleep [59].

Sodium oxybate (γ-hydroxybutyrate, **7**, Figure 8), an endogenous neurotransmitter involved in sleep regulation, is a rapid-acting hypnotic with a short half-life [57b, 58]. The exact mechanism by which **7** acts is unkown [58] but, in narcoplexy, GHB decreases cataplexy during the day and improves the quality of nighttime sleep, which seems to reduce daytime sleepiness [57b], without the adverse effects producted by the drugs currently used in therapy [60].

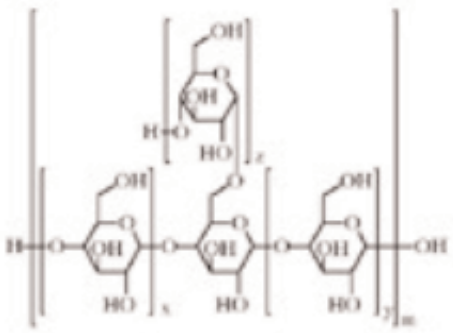
Figure 9



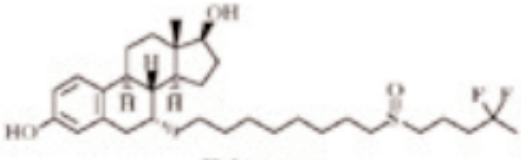
Aripiprazole
(Abilify™)



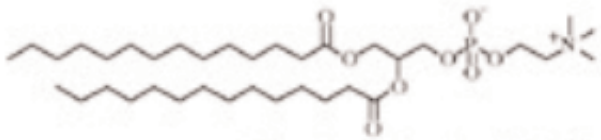
Olsartan medoxomil
(Benicar™)

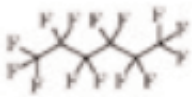


Icodextrin
(Extraneal®)

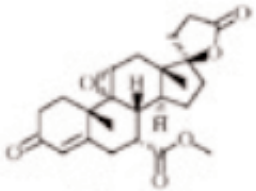


Fulvestrant
(Faslodex®)

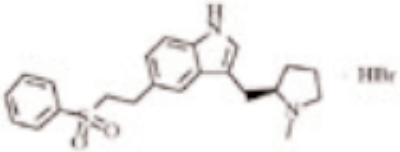




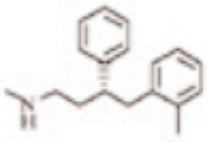
Dimyristoylphosphatidylcholine/Perflexane
(Imagent®)



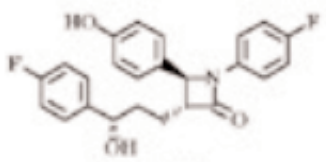
Eplerenone
(Inspra™)



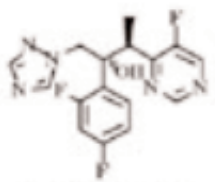
Eletriptan hydrobromide
(Relpax®)



Atomoxetine hydrochloride
(Strattera™)



Ezetimibe
(Zetia™)



Voriconazole
(Vfend®)

New Molecular Entities Approved in 2002 with Standard Review

Abilify™ (Bristol Myers Squibb & Otsuka)
Aripiprazole, 2, 5, 10, 15, 20 & 30 mg, tablet
Indication: atypical antipsychotic for the treatment of schizophrenia.
Date Approved: 15-11-2002

Benicar™ (Sankyo)
Olmesartan medoxomil, 5, 20 & 40 mg, tablet
Indication: angiotensin II receptor blocker for the treatment of hypertension.
Date Approved: 25-04-2002

Extraneal® (Baxter)
Icodextrin, 1.5, 2.0 & 2.5 L, 7.5% solution
Indication: peritoneal dialysis (PD) solution for single daily exchange for the long (8-16 hours) dwell during continuous ambulatory PD or automated PD for the management of chronic renal failure.
Date Approved: 20-12-2002 (orphan drug)

Faslodex® (AstraZeneca)
Fulvestrant, 250 mg, injection
Indication: estrogen receptor antagonist for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.
Date Approved: 25-04-2002 (also available in Italy [15])

Imagent® Kit for preparation of perflexane lipid microspheres, injectable suspension, i.v. (formerly *Imavist*) (Alliance Pharmaceuticals)
Dimyristoylphosphatidylcholine/perflexane, injectable suspension i.v.
Indication: ultrasound imaging agent for use in subjects with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.
Date Approved: 31-05-2002

Inspra™ (Pharmacia)
Eplerenone, 25, 50 & 100 mg, tablet
Indication: selective aldosterone blocker for the treatment of hypertension alone or in combination with other antihypertensives.
Date Approved: 27-09-2002

Relpax® (Pfizer)
Eletriptan hydrobromide, 20 & 40 mg, tablet
Indication: triptan anti-migraine agent for the treatment of acute migraine with or without aura in adults.
Date Approved: 26-12-2002 (also available in Italy [15])

Strattera™ (Lilly)
Atomoxetine 250 mg, capsule
Indication: non-stimulant, selective norepinephrine reuptake inhibitor for the treatment of attention deficit/hyperactivity disorder in children (ages six and older), adolescent and adults.
Date Approved: 26-11-2002

Vfend® (Pfizer)
Voriconazole, 50 & 200 mg, tablet;
200 mg, injectable suspension i.v.
Indication: antifungal for the treatment of invasive aspergillosis and serious fungal infections caused by the pathogens *Scedosporium apiospermum* and *Fusarium* spp., including *Fusarium solani*, in patients intolerant of or refractory to other therapy.
Date Approved: 24-05-2002 (also available in Italy [15])

Zetia™(Merck/Schering-Plough)
Ezetimibe, 10 mg, tablet
Indication: lipid altering drug for use alone or in combination with statins to reduce elevated total-cholesterol, LDL-C and Apo B in patients with primary hypercholesterolemia; for combination use with atorvastatin or simvastatin to reduce total-C and LDL-C, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in patients with homozygous familial hypercholesterolemia; and to reduce elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.
Date Approved: 25-10-2002

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