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NEWLY FDA-APPROVED DRUGS AND BIOLOGICS (JANUARY-DECEMBER 2004). PART 2

The aim of this review is to survey the new "molecular entities" (NME) drugs and new biological license applications (BLA) approved by the Food and Drug Administration (FDA) in the year 2004 (i.e., those not previously marketed in the United States of America). In Part 2 some of the drugs subject to "Priority Review" (i.e., those representing significant improvements compared with marketed products [1]) [10 NME, 35 references] will be considered. As for the drugs subject to "Standard Review" (i.e., those having therapeutic qualities similar to those of already marketed products [1]) (14 NME), only basic information (product, sponsor, date approved, indication, structural formula and availability in Italy) will be given [2]. Part 2 of the review follows the reviews about NME approved by the FDA in the years 1998-2003 and Part 1 of NME and BLA approved by FDA in 2004 [3].

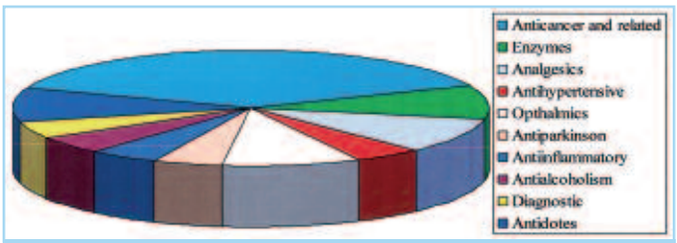

Fig. 1 - Therapeutic classes of NME and BLA approved by "priority review"

New Molecular Entities and Biological License Applications Approved in 2004 with Priority Review. Part 2

In order to offer an overview of the subject, the drugs have been divided into therapeutic classes, as can be seen in figure 1. Various anticancer and related drugs are present (as in 1998-2003), because of the great interest in the related diseases. In addition enzymes, analgesics, ophthalmics (as in 2001), diagnostics (as in 1998 and 1999), antidotes (as in 2003), an antihypertensive (as in 1999 and 2003), an antiparkinson, and drugs related to therapies for multiple sclerosis and alcoholism are included in the FDA-approved NME and BLA. In Part 2 analgesics, an antiparkinson, an antihypertensive, ophthalmics, diagnostics, antidotes and a drug related to therapy for alcoholism are reported.

Analgesic drugs

Lyrica® (Pfizer)
Pregabalin, capsules [4]
Indication: follow-on to Pfizer's *Neurontin* (gabapentin) for management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) [simultaneously approved via NDA 21-723 for treatment of postherpetic neuralgia (PHN)].
Date approved: 30-12-2004

Neuropathic pain is a chronic condition caused by injury to the nervous system, having many causes: the largest are related to DPN and PHN affecting an elevated number of diabetics or people who have suffered herpes zoster infection [4a, 4b, 5]. Treatment of DPN and PHN relies on nonpharmacological approaches (e.g. glycaemic control and other lifestyle intervention in the case of DPN or physical therapy, psychosocial intervention for PHN) but also on pharmacological control [4a, 4b]. The interventions of this type include a number of drugs such as tricyclic antidepressants and analgesics (recently duloxetine was introduced for DPN) [4a, 4b]. However, the necessary slow time and, in some cases, combination therapy increase various factors,

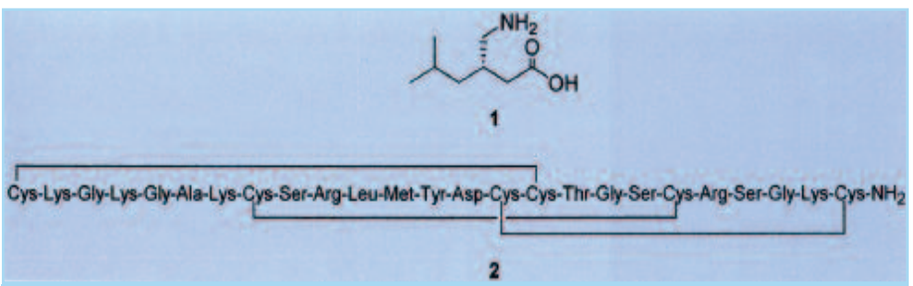

Fig. 2 - Analgesic drugs

such as the risk of drug-related adverse events [4a, 4b].
Pregabalin (**1**, Fig. 2), which was first synthesized as described in [6], is the *S*-(+) enantiomer of 3-aminomethyl-5-methylhexanoic acid, a molecule related to γ-amino butyric acid (GABA). **1** has a similar profile to that of the anticonvulsivant gabapentin, an alkylated analogue of GABA effective in the case of DPN or PHN, but shows a greater analgesic activity in rodent models of neurophatic pain [4a, 4b]. The mechanism through which **1** acts is not clear but recent findings indicate that binding to α2-δ protein, an auxiliary subunit of voltage-gated calcium channels, is a prerequisite for its action [4a, 4b]. The results of the randomized clinical trials of **1** suggest that beneficial effects can occur within the first week of treatment [5].

Prialt® (Elan)
Ziconotide, intratecal infusion [7]
Indication: N-type neuronal calcium channel blocker for the management of severe chronic pain in patients for whom intratechal therapy is warranted and who are intolerant of or refractory to other treatment, such as systemic analgesic, adjunctive therapies or intrathecal morphine.
Date approved: 28-12-2004

Intratechal administration of analgesics is usually tried only when standard therapy has failed [7a]. Morphine is used for treatment of chronic pain, baclofen in the case of spasticity; other opioid, ketamine, midazolam, clonidine and local anesthetics such as lidocaine and bupivacaine have been used intrathecally off-label, sometimes in combination [7a].
Ziconotide (**2**) is a synthetic equivalent of the ω-conopeptide MVIIA, firstly reported as a peptide component of the venom of *Conus magus* [7b, 8], whose sequence of amino acid is reported in Figure 2. **2** acts by inhibiting the activity of pain-sensing primary nociceptors by a direct blockade of N-type voltage-sensitive calcium channels [7b]. The pharmacological action of **2** is dependent on the intact disulfide bonds and a triple-stranded β-sheet stabilizing the structure and confering additional resistance to peptidase in addition to possibly enhancing binding potency and selectivity [7b]. The structure of **2** has several implications for its use as a therapeutic [7b]. Psychiatric symptoms and neurological impairment may occur during treatment with **2** mainly because of blocking of other nerve functions [9].

Antiparkinson drugs

Apokyn™ (Bertek) (orphan drug)
Apomorphine hydrochloride, injection [10]
Indication: dopamine (DA) receptor agonist for acute, intermittent treatment of hypomobility and "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease (PD).
Date approved: 20-04-2004 (available also in Italy [11])

PD is characterized by bradykinesia, rigidity and tremor at rest. Progressively, postural instability develops and contributes to episodes in which a slow, shuffling gait transforms into a rapid, festinating gait and a tendency to fall forward. Retropulsion with a tendency to fall backward also occurs [12]. PD is a chronic disorder resulting from the loss of pigmented mesostriatal dopaminergic neurons linking the substantia nigra to the neostriatum [10b], so replacement of DA is the major medical approach to treating its motor symptoms [12]. Levodopa/carbidopa is used in all the cases of advanced PD with positive effect during the first two to five years but after this period can become increasingly more difficult to manage the diseases in advanced states [10a, 12]. Lack of voluntary muscle movements during the night and waking in "off" state are frequent states resulting also in "wearing off" episodes: some patients develop sudden, unpredictable fluctuations between mobility and immobility (the "on-off" effect) [10a, 12]. Once "off" fluctuations have developed, a number of pharmacological approaches are used to minimize their occurence, including increasing the frequency and/or dose of levodopa/carbidopa, adding a COMT or selective MAO-B inhibitor as an adjunct to levodopa/carbidopa therapy, and adding amantadine or an oral DA agonist [12].
Apomorphine hydrochloride (**3**, Fig. 3), a catecholamine derivative which was synthesized in the Nineteenth century yet [13], is a potent, short-acting DA agonist having a balanced affinity for D_1 and D_2 receptors, a combination providing a clinical effect similar to that of levodopa [12]. The use of subcutaneous **3** for the treatment of reversing sudden, unexpected and refractory levodopa-induced "off"

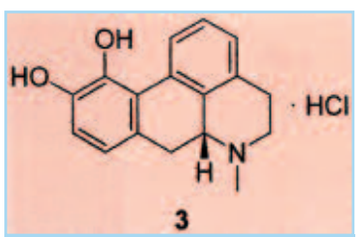

Fig. 3 - Antiparkinson drugs

states in advanced PD reduces consistently the time spent "off" [10b]. In addition, continuous infusions motor fluctuactions and dyskinesia, and improve motor scores while "on" [10b]. Results of clinical trials also comparative of **3** and levodopa are reported [10b, 12].

Antihypertensive/vasodilator drugs

Ventavis® (CoTherix)
Iloprost, inhalation solution [14]
Indication: inhalation prostacyclin for treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in patients with NYHA Class III or IV symptoms.
Date approved: 29-12-2004 (available also in Italy [15])

PAH is characterized by increased, above-normal blood pressure within the pulmonary arterial system [16, 3e]. 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 [16, 3e]. 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 [16, 3e]. Besides this diagnostic classification, patients should be stratified according to their functional capacity, which is important to determine prognosis and to guide therapeutic efforts [17]. The current treatment algorithm is restricted to patients in functional classes III and IV, who represent the largest population among PAH patients, and include oral anticoagulants, diuretics, calcium blockers and endothelin receptor antagonists [17]. In addition, prostacyclin derivatives, such as intravenous epoprostenol and subcutaneous treprostinil, are present in clinical pratical [17, 3e].
Iloprost (**4**, Fig. 4) is a prostacyclin derivative synthesized as described in [18]. **4** has a pharmacological profile similar to epoprostenol but a longer serum half-life (20-30 *vs* 2-3 min) because of a greater chemical stability and a different route of administration; these situations induce advantages related to time of administration and selectivity for the pulmonary vascular system with consequent reduction of systemic adverse effects, respectively [14, 17]. Inhaled treprostinil is being evaluated in clinical trials because of the longer half-life in comparison to **4** [17].

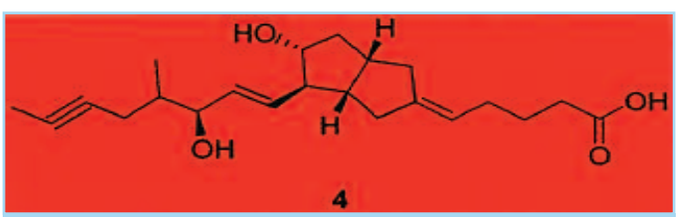

Fig. 4 - Antihypertensive/vasodilator drugs

Ophthalmic drugs

Macugen® (Eyetech/Pfizer)
Pegaptanib sodium, injection [19]
Indication: vascular endothelial growth factor antagonist for treatment of neovascular (wet) age-related macular degeneration (AMD).
Date approved: 17-12-2004

AMD is a deterioration of the central part of the retina classified in two forms: nonexudative (dry) and exudative (wet), which is characterized by choroidal neovascularization, leading to leakage of blood or serum, detachment of the retinal pigment epithelium and fibrovascular scarring and is responsible for most cases of severe vision loss [19a, 20]. Laser photocoagulation may be effective in delaying the progression of the disease but lacks specificity, is associated with retinal destruction causing impaired visual function and progression of retinopathy; however, photodynamic therapy, which involves laser ablation of new choroidal vessels is only helpful in a subset of neovascular lesions and repeated treatments are often required [21]. Angiogenesis, a complex process defined as the formation of new blood vessels from preexisting vasculature, has a key role in normal development but also in several diseases, such as cancer and neovascular eye disorders [20]. Vascular endothelial growth factor (VEGF) is a key positive regulator of angiogenesis and has been implicated as a major mediator of pathological ocular neovascularization [20].
Pegaptanib sodium (**5**), whose structural formula is reported in [19e], is a covalent conjugate of an oligonucleotide twenty-eight nucleotides in length that terminates in a pentylamino linker, to which two twenty-kilodalton monomethoxy polyethylene glycol (PEG) units are covalently attached via the two amino groups on a lysine residue [19e]. **5**, an aptamer (that is an oligonucleotide isolated from randomized libraries of RNA, DNA or modified nucleic acids that binds with high affinity and specificity to molecular targets) designed for binding specifically extracellular $VEGF_{165}$, possesses an extremely high affinity for this isoform [22]. **5** is the first aptamer approved and the first antiangiogenic agent approved for neovascular macular degeneration [19b, 23].

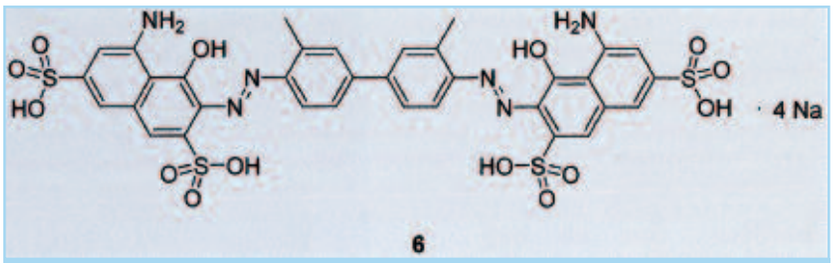

Fig. 5 - Opthalmic drugs

VisionBlue® (Dorc)
Tryptan blue 0.06%, ophthalmic solution
Indication: selective tissue staining agent for use as an aid in ophthalmic surgery by staining the anterior capsule of the lens.
Date approved: 16-12-2004

A cataract is a clouding of the eye's naturally clear lens developing as a normal process of aging or from eye injuries or diseases, such as diabetes, or medications [24]. Currently, there is no proven way to prevent the development of cataracts other than controlling medical conditions that may be the cause, even if antioxidants like β-carotene and vitamins C and E have been identified as reducing the risk of developing and slowing the progression of this disease [25]. Cataracts are treated with surgery because there is no medicine or other treatment that can dissolve or remove cataracts [25].
Tryptan blue (**6**, Fig. 5) is a naphthalenedisulfonic acid derivative synthesized some decades ago [26]. **6** favours the action of eye surgeons removing cataract because of its ability to make the anterior lens capsule easier to visualize through selective staining, manipulate and remove the cloudy lens through a surgical incision [24].

Antialcoholism drugs

Campral® (Lipha)
Acamprosate calcium, tablet [27]
Indication: oral tablet for maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation.
Date approved: 29-07-2004

Alcohol dependence is a chronic disorder characterized by drinking that is in excess of that intended, to an extent that interferes with other activities and/or responsibilities and is often marked by additional criteria of tolerance and/or withdrawal [27a, 27c]. In fact, alcohol affects brain function by interacting with multiple neurotrasmitter systems, thereby temporarily disrupting the balance between excitatory and inhibitory neurotrasmitters (glutamate/GABA) in favour of inhibitory influences [27a]. With long-term, chronic exposure, the brain compensates by upregulating excitatory mechanisms while concurrently decreasing inhibitory neurotrasmission to help restore equilibrium; persistent similar action, however, ultimately results in neuroadaptive changes that eventually lead to alcohol tolerance and dependence and, upon removal of alcohol, withdrawal [27a]. Key requirements for the management of alcohol-dependent adults are the need to aid withdrawal, maintain abstinence after detoxification and reduce the craving for alcohol [27c]. Psychosocial support without complementary pharmacological treatments has had only limited success in achieving prolonged abstinence [27a]. Naltrexone, a long-acting oral opiate antagonist and disulfiram, interfering with metabolism of alcohol, has been approved in recent years [27d].
Acamprosate calcium (**7**, Fig. 6) is a taurine derivative with a structural resemblance to GABA firstly studied in [28]. Recent evidence suggests that **7** acts by interacting with excitatory glutamatergic neurotrasmission, in particular as an antagonist of the metabotropic glutamate receptor subtype 5 (mGluR5) [27b]. This action facilitates the maintenance of abstinence and reduces the negative symptomatology associated with the acute postwithdrawal period in detoxified alcohol-dependent patients [27c]. In addition, **7** may also decrease the frequency of drinking and reduce alcohol consumption if a relapse has occurred [29]. In recent years a number of studies comparing **7** with naltrexone or disulfiram have been reported (for examples see [27d, 30]). Recent advances and future perspective are included in [29].

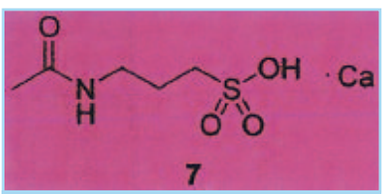

Fig. 6 - Antialcoholism drugs

Diagnostics

ChiRhoStim™ (ChiRhoClin) (orphan drug)
Human secretin, injection
Indication: human secretin to aid the diagnosis of pancreatic exocrine dysfunction and gastrinoma, and facilitate the identification of the ampulla of vater and accessory papilla during endoscopic retrograde cholangiopancreatography (ERC).
Date approved: 09-04-2004

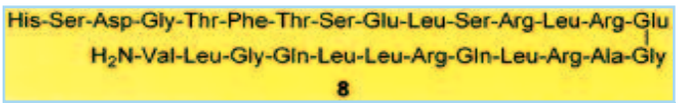

Fig. 7 - Diagnostics

An efficient diagnosis is a fundamental step in the cure of pathologies such as those involving pancreatic disfunctions, gastrinoma (a gastric and abdominal lymphonodes tumor associated with gastroenterological disorders known as Zollinger-Ellison syndrome [31]) and other situations related to utilization of radiographic instruments as ERC, an endoscope used to detect any abnormalities in the duct draining the liver and pancreas [32].
Human secretin (**8**, Fig. 7) is a purified synthetic peptide with an amino acid sequence identical to the naturally gastrointestinal hormone produced by cells in the duodenum in response to acidification [33]. The primary action of **8** is to increase the volume and bicarbonate content of secreted pancreatic juices, gastrin release in patients with gastrinoma (no change, or only small changes, in serum gastrin occurs in normal patients and in patients with duodenal ulcer disease) [33].

Antidotes

Pentetate calcium trisodium (Pharma Hameln GmbH)
Pentetate calcium trisodium [calcium-diethylenetriaminepentacetate (Ca-DTPA)], injection
Indication: chelating agent for treatment of internal radiation contamination with plutonium, americium or curium; for use within 24 hours of exposure, with use of Zn-DTPA for maintenance therapy if available (if continued use of Ca-DTPA is required zinc supplements should be given).
Date approved: 11-08-2004

Pentetate zinc trisodium (Pharma Hameln GmbH)
Pentetate zinc trisodium (Zn-DTPA), injection
Indication: chelating agent for treatment of internal radiation contamination with plutonium, americium or curium; for use within 24 hours of exposure if Ca-DTPA is not available and for use as maintenance therapy.
Date approved: 11-08-2004

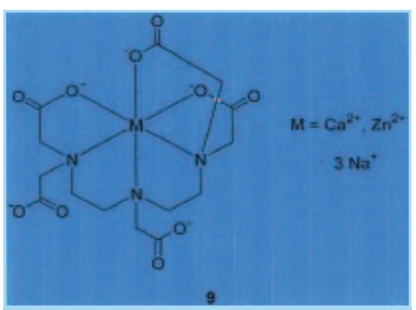

Fig. 8 - Antidotes

A variety of routes including ingestion, inhalation, or direct contact through wounds can determine internal contamination with transuranium elements (plutonium, americium or curium) from laboratory or industrial accidents or through terrorist attacks [34].
Ca- and Zn-DTPA (**9**, Fig. 8) act by forming stable chelates via the exchange of calcium or zinc for above-mentioned transuranium elements, which are metals of greater binding capacity [35]. The radioactive chelates are then excreted by glomerular filtration into the urine [35].

New Molecular Entities Approved in 2004 with Standard Review (Fig. 9)

Apidra® (Aventis)
Insulin glulisine [rDNA origin], injection
Indication: rapid-acting rDNA insulin analog to treat adult patients with diabetes mellitus for the control of hyperglycemia.
Date Approved: 16-04-2004

Cymbalta® (Lilly)
Duloxetine hydrochloride
Indication: serotonin-norephinephrine reuptake inhibitor for treatment of major depressive disorder.
Date Approved: 03-08-2004

Enablex® (Novartis)
Darifenacin hydrobromide
Indication: selective M_3 muscarinic antagonist for treatment of overactive bladder.
Date Approved: 22-12-2004

Fosrenol® (Shire)
Lanthanum carbonate hydrate, chewable
Indication: non-calcium, non-aluminum based phosphate binder for reduction of elevated blood phosphate levels in patients with end-stage renal disease.
Date Approved: 26-10-2004

Ketek® (Aventis)
Telithromycin, tablet
Indication: oral ketolide antibiotic for use in patients 18 years and

older to treat acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis*; acute bacterial sinusitis due to *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* or *Staphylococcus aureus*; and community-acquired pneumonia of mild to moderate severity due to *S. pneumoniae* (including multi-drug resistant isolates), *H. influenzae*, *M. catarrhalis*, *Chlamydophila pneumoniae* or *Mycoplasma pneumoniae*.
Date Approved: 01-04-2004 (available also in Italy [11])

Lunesta™ (formerly *Estorra*) (Sepracor)
Eszopiclone, tablet
Indication: non-benzodiazepine hypnotic for treatment of insomnia.
Date Approved: 15-02-2004

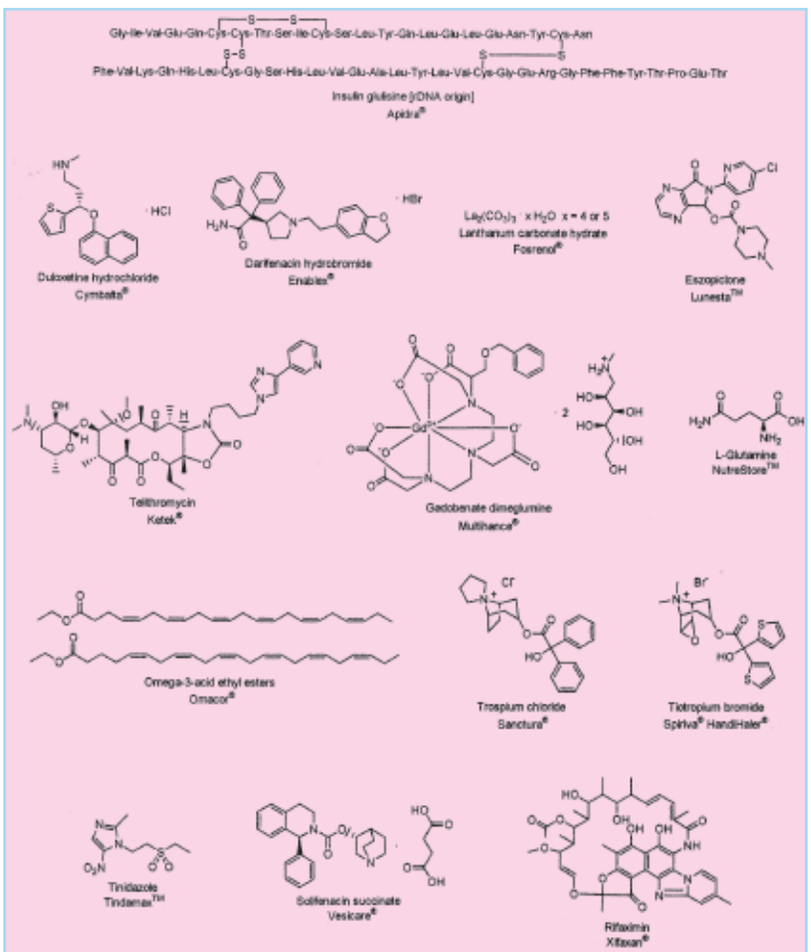

Fig. 9 - NME approved by "standard review"

Multihance® (Bracco)
Gadobenate dimeglumine, injection
Indication: paramagnetic positive contrast agent for magnetic resonance imaging of the central nervous system.
Date Approved: 23-11-2004 (available also in Italy [11])

NutreStore™ (Nutritional Restart)
L-glutamine, powder for oral solution
Indication: amino acid tratment of short bowel syndrome in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone that is approved for this indication.
Date Approved: 10-06-2004

Omacor® (Ross)
Omega-3-acid ethyl esters, capsule
Indication: lipid-regulating agent for the treatment of hypertriglyceridemia in adults.
Date Approved: 10-11-2004

Sanctura® (Invedus)
Trospium chloride, tablet
Indication: oral antispasmodic, antimuscarinic for treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency.
Date Approved: 28-05-2004 (available also in Italy [11])

Spiriva® *Handihaler*® (Boehringer Ingelheim)
Tiotropium bromide, inhalation
Indication: once-daily inhaled bronchodilator for long-term treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.
Date Approved: 30-01-2004 (available also in Italy [11])

Tindamax™ (Presutti) (orphan drug)
Tinidazole, tablet
Indication: antiprotozoal for treatment of trichomoniasis, giardiasis, amebiasis and amebic liver abscess.
Date Approved: 17-05-2004 (available also in Italy [11])

Vesicare® (Yamanouchi)
Solifenacin succinate, tablet
Indication: selective M_3 muscarinic antagonist for treatment of overactive bladder symptoms of urinary frequency, urge urinary incontinence and urgency.
Date Approved: 19-11-2004

Xifaxan® (Salix)
Rifaximin, tablet
Indication: broad-spectrum, gastrointestinal site-specific antibiotic for treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli*.
Date Approved: 25-05-2004 (available also in Italy [11])

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