Newly FDA-Approved Drugs (January-December 2000)

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 2000 (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, 53 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) (18 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 and in 1999 [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. As in 1998 and 1999, antitumor and antiviral drugs are included due to the great interest in the treatment of these pathologies. Other important fields of research are represented by newly FDA-approved drugs given priority review, that is antibacterial drugs, in primis, and also ophthalmic, antiprogestin and other classes. Interestingly, an anti-inflammatory drug approved in 2000 has been withdrawn from the market in the same year.

Antiviral drugs

Kaletra® (Abbott Laboratories)
Lopinavir/ritonavir, 133.3 mg/33.3 mg, capsule and 80 mg/20 mg, oral solution [3]. Indication: co-formulation of the two protease inhibitors for treatment of HIV infection in combination with other antiretrovirals in adults and pediatric patients six months and older.
Date approved: 15-09-2000

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 it begins 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 to a minimum the resistance of the virus, recommended therapies foresee the administration of multi-drug treatments (named highly active antiretroviral therapy, HAART) employing several different drugs, e.g., two nucleoside reverse transcriptase inhibitors in association with a non-nucleoside reverse transcriptase inhibitor 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, antiretroviral therapy including a PI could fail because of limits in the detection of a sensitive viral load or the inability of patients to sustain an undetectable viral load for prolonged periods since a high degree of compliance is needed to maintain viral suppression. In addition, many currently available HIV PIs have low oral bioavailability and a short half-life, and pharmacokinetic interactions (with food, plasma proteins or other medications) are common.
Lopinavir/ritonavir (**1**, Figure 2) is the first fixed-dose combination of PIs approved by the FDA for the treatment of

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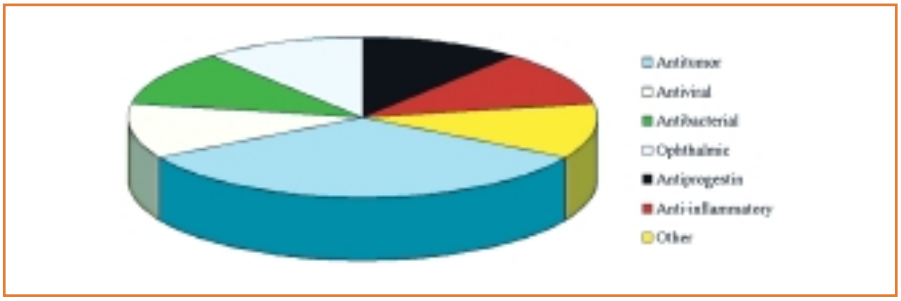

Figure 1 - Therapeutic classes of NME approved by "priority review"

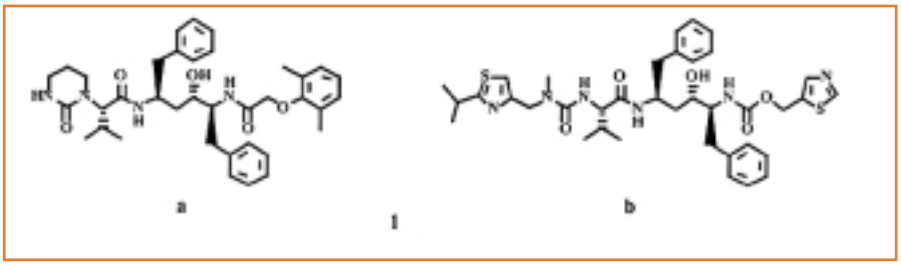

Figure 2

HIV infection. **1** consists of a 4:1 mixture (w/w) of two PIs, both of which are chemically based on the same hydroxyethylene dipeptide: lopinavir (**1a**), a new drug available only in this combination and which is synthesized as described in [7], and ritonavir (**1b**), a previously approved PI [8]. **1a** is considered a second-generation PI which is active against viruses resistant to the previously released PIs, including amprenavir, a PI approved in 1999 [2b]. **1** takes advantage of the pharmacokinetic interaction between **1a** and **1b**. In fact, whereas **1a** is metabolized rapidly by the hepatic isoenzyme cytochrome P450 CYP3A4 [9], **1b** is a potent inhibitor of CYP3A4 activity and raises plasma levels of **1a**, thus exceeding inhibitory concentrations for many strains, even some which are resistant to other PIs [10]. The bioavailability of **1** is increased by food [10]. Kaletra® is available also in Italy.
An overview of the current status of HIV pathology, perspectives on retroviral resistance and new developments in anti-HIV chemotherapy are reported in [4 and 11 a,b,c, respectively].

Antibacterial drugs

Zyvox® (Pharmacia)
Linezolid 400 and 600 mg, tab.; 200 mg/100 mL, 400 mg/200 mL and 600 mg/300 mL, inj.; and 100 mg/5 mL, oral suspension [12].
Indication: oxazolidinone antibiotic for treatment of adult patients with vancomycin-resistant *E. faecium* infections, nosocomial-acquired pneumonia (including cases due to methicillin-resistant *S. aureus*), community-acquired pneumonia, and complicated and uncomplicated skin and skin structure infections.
Date approved: 18-04-2000

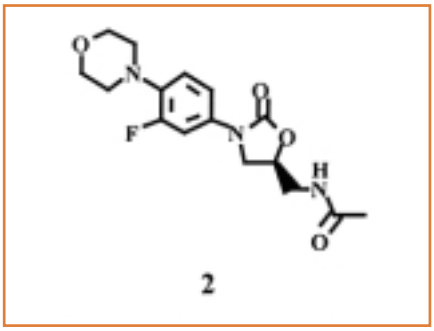

Figure 3

Antibiotic resistance has proven to be a severe problem, because the limited number of antibacterial agents that can be used effectively to treat the infections leads to an increase in morbidity and mortality. Various strategies have been followed to obviate this situation, including structural modifications to known drugs (e.g. new macrolides and quinolones), the use of compounds currently administered in combination with agents addressing the resistance mechanism (e.g. β-lactam with a β-lactam inhibitor), or the designing of novel classes of antimicrobial agents with new mechanisms of action that could potentially avoid cross-resistance [12f]. As to the last route, a chemically distinct class of synthetic antibiotics employing a unique mechanism of action, the oxazolidinones, was discovered during random screening tests and investigated in recent times for the treatment of serious multidrug-resistant Gram-positive bacterial infections caused by strains of staphylococci, streptococci, and enterococci [13].
Linezolid (**2**, Figure 3) is a morpholinyl analogue of piperazinyl oxazolidinone, synthesized as described in [14]. **2** exerts its bacteriostatic action by inhibiting protein synthesis: it seems that **2**, like other drugs in this class, blocks the formation of *N*-formylmethionyl-tRNA-ribosome-mRNA ternary complex involving 30S and 70S ribosomes through direct binding to the bacterial 50S ribosomal subunit [15].
Since **2** does not affect the elongation and/or termination of the translation phase, cross-resistance with other currently available antimicrobial agents has not been reported [16]. **2** is the second drug to be approved by the FDA for treatment of vancomycin-resistant enterococci (VRE) but, unlike quinupristin/dalfopristin (Synercid®), an i.v. streptogramin marketed since 1999 [2b], it can be administered per os due to its 100% bioavailability. Thus, **2** is the only oral agent available in the US with reliable activity against methicillin-resistant *Staphylococcus aureus* and VRE.
2, like eperezolid, another oxazolidinone derivative currently undergoing clinical trials, was designed on the basis of information derived from a set of three lead compounds: DuP 721, a clinical candidate chemically differing from **2** in a substitution on the aryl ring but which was not developed because of its toxicity, (±)-PNU-85112, an indoline oxazolidinone with a good safety profile and E-3709, a second-generation phenyloxazolidinone, as well as the antibacterial class of fluoroquinolones [12f]. Studies of structure-activity relationship of **2** revealed that: a) the *N*-aryl group is required for activity and the electron-donating nitrogen atom is well tolerated and often improves the safety profile, b) fluorination of the phenyl ring often improves antibacterial activity/efficacy, c) the (*S*)-configuration of the stereogenic center is necessary for antibacterial activity and d) the acylaminomethyl group in position 5 is essential for good activity [12f]. A further aim which needs to be addressed is to enhance potency and expand spectrum of activity to include the Gram-negative organisms *Haemophilus influenzae* and *Moraxella catarrhalis*. Some of these studies are reported in [12f, 17]. A recent report about the causes and the potential solutions to the increasing and accumulating threat of antibacterial resistance is given in [18].

Antitumor drugs

Mylotarg® (Wyeth-Ayerst, developed with Celltech Chiroscience) (orphan drug)
Gemtuzumab ozogamicin, inj. [19].
Indication: engineered human antibody linked to the cytotoxic drug calicheamicin for treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are 60 or older and who are not considered candidates for cytotoxic chemotherapy.
Date approved: 17-05-2000 (accelerated approval)

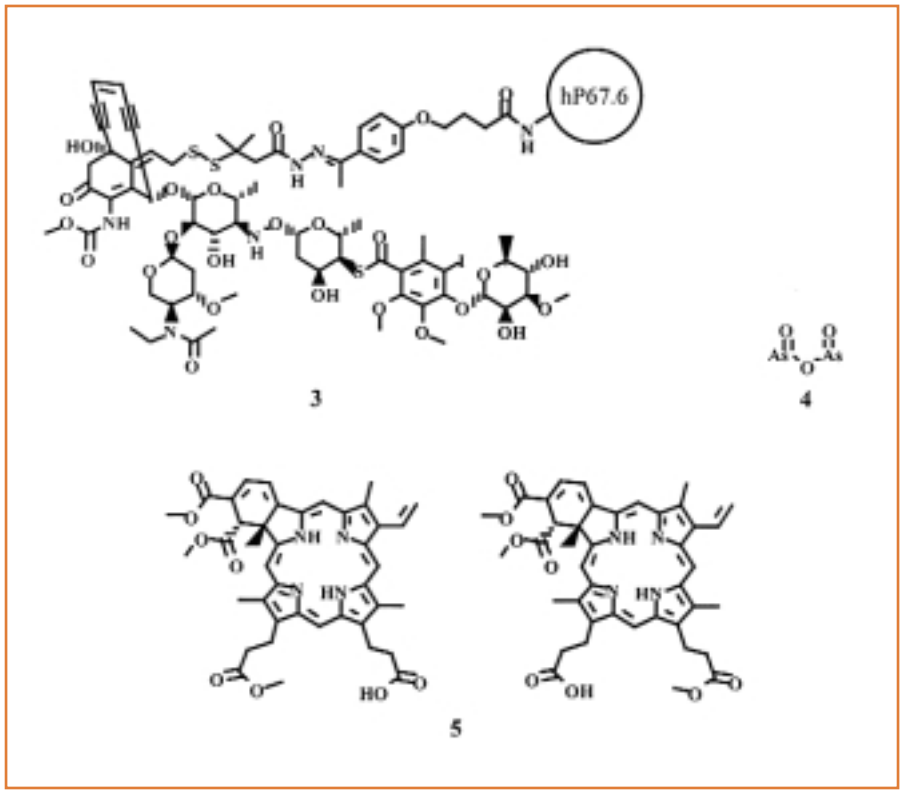

Figure 4

Trisenox® (Cell Therapeutics) (orphan drug)
Arsenic trioxide, 10 mg/mL (1 mg/mL) ampule, inj.
Indication: anticancer agent for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15:17) translocation or PML/RAR-alpha gene expression.
Date approved: 25-09-2000

Myeloid or granulocytic leukemia is a blood disease involving the neoplastic transformation of granulocytes. It comprises acute myeloid leukemia (AML) and its subtype form, acute promyelocytic leukemia (APL). Treatment of AML and APL involves very aggressive combinations of nonspecific chemotherapeutic drugs that do not discriminate between healthy and disease cells; recently, some targeted strategies that exploit the unique biological characteristics of myeloid leukemia cells have been developed.
AML is an aggressive form of cancer characterized by a rapid accumulation of abnormal white cells in the blood and bone marrow, resulting in severe anemia, increased risk of infections and recurrent hemorrhages, and preventing normal marrow from growing and functioning properly [19].
Although chemotherapy induces a first remission in a large number of adult patients with AML, this therapeutic strategy is accompanied by side effects and relapses within two years [20]. As a result, curative therapy for AML remains unsatisfactory. However, three recent advances may play an important role in determining how AML is treated in the near future. First, antibody-target chemotherapy in which the cytotoxic agent is linked to an antibody recognizing the leukemic cells and antineoplastic drugs are delivered to malignant cells but not most normal ones [20a-22]; second, modern molecular methods which have improved the ability of physicians to identify minimal residual disease in patients who appear to be in remission [22]; third, microarray gene expression technology that allows for the simultaneous study of thousands of genes [22].
As regards antibody therapy, the CD33 antigen is an appropriate target because AML blast cells express the CD33 antigen in more than 90% of patients, whereas hematopoietic stem cells, lymphoid cells, and non-hematopoietic cells do not express the CD33 antigen [20a, 23].
Gemtuzumab ozogamicin (**3**, Figure 4) is the first antibody-targeted chemotherapy agent using monoclonal antibody technology for the treatment of relapsed AML in adults. **3**, prepared as described in [24], combines the γ_1 derivative of calicheamicin, a potent cytotoxic antibiotic linked to a recombinant humanized IgG4 κ antibody that binds specifically to the CD33 antigen. Once the anti-CD33 antibody portion of **3** binds to the CD33 antigen, the complex is internalized by CD33 cells. The calicheamicin derivative is then released inside the lysosomes of the myeloid cell and binds to DNA in the minor groove, resulting in DNA double-strand breaks and cell death by apoptosis [20a, 25].
Interestingly, a conceptual analog to **3**, namely lintuzumab (HuM195), is undergoing clinical trials by the FDA [19].
APL is characterized by blockage of leukemic cells at the promyelocytic stage of granulocytic differentiation, genotypically caused by the promyelocytic leukemia/retinoic acid receptor α (PML/RARα) oncogenic fusion protein, a result of t(15:17) translocation (the most common form of translocation) [26]. Current therapy with all-*trans*-retinoic acid (ATRA) plus an anthracycline with or without cytosine-arabinoside has yielded complete response rates of ≥85% and long-term disease-free survival rate ≥70% [27]. However, multiple issues remain to be addressed [27]. Arsenic trioxide (**4**, Figure 4) determines disease remission in APL patients by inducing differentiation through RARα/RXR pathways, and apoptosis, at low or high concentrations, respectively; in spite of this, we are still just beginning to understand the mode of action of **4** at the molecular level [27, 28]. Therapy with **4** achieved a 70% complete response rate in APL patients who were refractory or had relapsed after prior treatment with cytotoxic chemotherapy and ATRA [29]. Interestingly, since **4** and ATRA target the PML-RARα fusion protein and cause remission of APL through distinct mechanisms of action, suggesting the possibility of synergic effects between the two drugs [28].

Visudyne® (CIBA Vision, QLT Photo Therapeutics co-developed and will manufacture)
Verteporfin, inj. [30].
Indication: light-activated therapy for treatment of age-related macular de-

generation in patients with predominantly classic subfoveal choroidal neovascularization.
Date approved: 12-04-2000

Age-related macular degeneration (AMD) is a degenerative eye disease. In neovascular AMD, which is characterized by subfoveal choroidal neovascularization (CNV), a rapid growth of abnormal blood vessels leads to a progressive and irreversible loss of central vision over a period of five years [31]. At present, since the pathogenesis of AMD is still unclear, preventive treatments do not exist [32]. Thermal laser photocoagulation, a technique introduced in the 1980s as CNV therapy, is suitable for only a small proportion of patients and, in addition, can cause nonselective necrotic damage and irreversible loss of visual acuity [31]. As a consequence, photodynamic therapy (PDT) has been investigated. PDT is a treatment modality in which a nontoxic light-sensitive compound called a photosensitizer is administered by intravenous infusion and subsequently activated by light exposure to produce photochemical effects in the target area [31]. PDT has the potential advantage of dual selectivity: firstly, there is a preferential concentration of the photosensitizer in the target tissue and, secondly, the light irradiation is directed toward and confined to the specific target area [31]. The first-generation photosensitizers licensed for use porfimer sodium has some limitations [31].
Verteporfin (**5**, Figure 4) is a benzoporphyrin derivative consisting of two regioisomers, synthesized as described in [33]. **5**, a second-generation light-activated drug for PDT, is the first available photosensitizing agent indicated for use and represents a major milestone in ophthalmology since previous treatments for AMD did not allow the preservation of existing vision. **5** is activated by low-intensity, nonheat-generating laser light at a wavelength of around 690 nm, enabling better tissue penetration, rapid and selective accumulation by endothelial cells in neovasculature and rapid clearance from the body [31]; activation of **5** leads to the generation of cytotoxic oxygen species such as singlet oxygen and free radicals, which can cause cytotoxic damage mainly through thrombus formation and selective vascular occlusion [31]. Visudyne® is available also in Italy.

Ophthalmic drugs

Rescula® (Ciba Vision)
Unoprostone isopropyl 0.15%, ophthalmic solution.
Indication: synthetic docosanoid for lowering of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another IOP-lowering medication.
Date approved: 03-08-2000

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 [34]. The course of this disease can be aggravated by an elevated intraocular pressure (IOP), an important risk factor. IOP is maintained by the balance between inflow and outflow of aqueous humour in the eye; the elevated IOP is the result of an impaired outflow but treatment, both surgical and medical, can be aimed at inflow as well as outflow [35]. Prostaglandin (PG) analogues represent a new class of ocular hypotensive drugs.
Isopropyl unoprostone (**6**, Figure 5) is a PG analogue, based on $PGF_{2\alpha}$, synthesized as described in [36]. Like the other structures of this class, **6** would appear to increase the uveoscleral outflow of ocular aqueous humour, but its mechanism of action is not yet fully understood. However, it has been reported that **6** has only a weak agonist activity for the FP and almost no affinity for EP_1 and EP_2 prostanoid receptors, in contrast with latanoprost, another PG analogue marketed in the US since 1996 as Xalatan® [37]. This is the probable explanation of why latanoprost administered once daily was found to be significantly more effective in reducing IOP than was **6** administered twice daily [38].
Interestingly, the FDA has announced the approval of two new drugs to treat the elevated IOP which is often associated with glaucoma, that is Lumigan® (bimatoprost) 0.03% and Travatan®

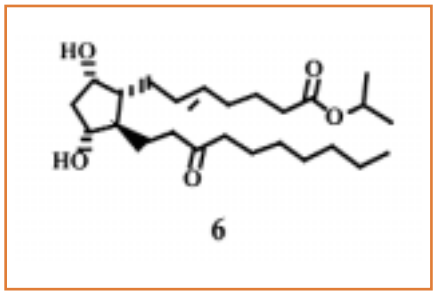

Figure 5

(travoprost) 0.004%, both of which contain a PG analogue [39].

Antiprogestin drugs

Mifeprex® (Population Council/Danco Laboratories)
Mifepristone (RU-486) 200 mg, tab.
Indication: abortifacient for medical termination of intrauterine pregnancy through 49 days of pregnancy; to be used with misoprostol, taken two days after mifepristone.
Date approved: 28-09-2000

Progesterone is required for both pregnancy development and maintenance. After ovulation, the corpus luteum secretes progesterone to create a secretory endometrium that is appropriate for embryo implantation. Once implantation has occurred, progesterone suppresses uterine contraction. Continuation of pregnancy is dependent on luteal progesterone until placental secretion of progesterone is sufficient, typically by the seventh week after conception [40].
Mifepristone (**7**, Figure 6), a derivative of 19-nor-testosterone synthesized as described in [41], is a potent progesterone receptor antagonist. The blocking of uterine progesterone receptors resulting from administration of **7** causes an increase in uterine contractility leading to embryo detachment from the uterine wall; this event triggers a series of physiological processes increasing the levels of uterine prostaglandins (PGs), which produce uterine contractions and cause expulsion of the embryonic tissue. **7** in association with a PG (i.e., misoprostol) is effective in around 95% of women: in the remaining 5% surgical abortion is necessary for completion of the procedure [40]. **7** is the first FDA-approved method for medical abortion in the US, although it has been available for use in other countries since for many years. Its approval has reopened the debate of the opportune-

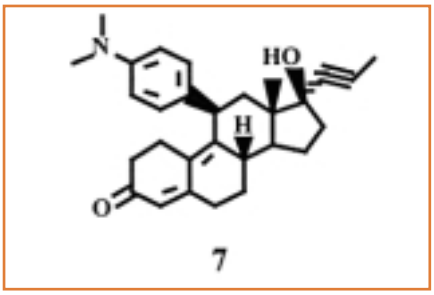

Figure 6

ness of abortion as discussed in [42].
Since the discovery of **7** much effort has been aimed at optimizing the structural requirements of antiprogestin compounds related to **7**; some of these studies are reported in [43].

Anti-inflammatory drugs

Lotronex® (Glaxo Wellcome)
Alosetron hydrochloride 1 mg, tab. [44].
Indication: 5-HT_3 receptor antagonist anti-inflammatory for treatment of irritable bowel syndrome in women whose predominant symptom is diarrhea.
Date approved: 09-02-2000 (withdrawn from market 28-11-2000)

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 the Rome II criteria [45]. IBS 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 [46]. 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 [45a], and pharmacological treatments recommended for patients with moderate to severe symptoms. An overview of possible therapies for IBS is shown in [45]. The rationale for using serotonin (5-hydroxytryptamine, 5-HT) receptor ligands in the treatment of IBS is based on the fact that 5-HT, which is released by gut mucosal enterochromaffin-like cells, lowers visceral pain thresholds by stimulating extrinsic enteric sensory nerves; in particular, antagonists of 5-HT_3 receptors, predominantly present in this area, increase these thresholds [47].
Alosetron hydrochloride (**8**, Figure 7), an indole derivative synthesized as described in [48], is the first 5-HT_3 receptor antagonist that has been developed for diarrhea-predominant IBS, specifically in women, as reported in [49]. The debate about the effects of **8** was generated [50]. In November 28, 2000, Glaxo Wellcome decides to withdraw Lotronex® from the market [51]. In fact, the FDA analyses of the post-marketing reports of serious adverse effects, included five reports of death or intestinal damage resulting from reduced blood flow to the intestine (ischemic colitis), as well as several obstructed or ruptured bowels (complications of severe constipation) [51].

Other drugs

Skin Exposure Reduction Paste Against Chemical Warfare Agents (*SERPACWA* U.S. Army Medical Research and Material Command)
Perfluoroalkylpolyether/polytetrafluoroethylene, paste
Indication: agent for use in conjunction with Mission-Oriented Protective Posture gear to reduce or delay the adsorption of chemical warfare agents through the skin when applied prior to exposure.
Date approved: 17-02-2000

The protective overgarment ensemble utilized against chemical warfare agents (CWA), consisting of protective suit, face mask, gloves and overboots, is unable to provide complete protection because leaks can occur through the enclosures around the wrists, lower legs (boot tops), neck and chin under the hood of the face mask [52].
SERPACWA (**9,** Figure 8) is composed of a 50:50 mixture of a perfluoroalkylpolyether (PFPE) and a polytetrafluoroethylene (PTFE) [53]. **9** acts as a physical barrier against a variety of CWA including sulfur mustard (a blistering agent), the nerve agents soman, thickened soman (TGD), and VX, T-2

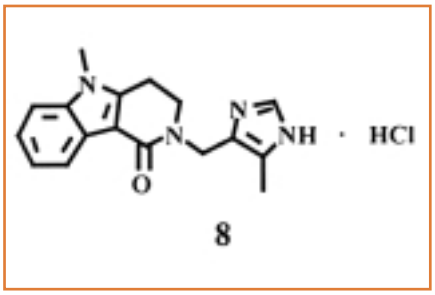

Figure 7

mycotoxin (a skin necrosis agent) and CS (a riot control tear gas), but it is not effective unless used in conjunction with Mission-Oriented Protective Posture agents [53].

NME approved in 2000 with Standard Review (Figure 9)

Abreva Cream® (Avanir Pharmaceuticals, SmithKline Beecham Consumer Healthcare will market)
Docosanol 10%, cream
Indication: OTC topical treatment for oral-facial herpes.
Date approved: 25-07-2000

Acova® (formerly Novastan®) (Texas Biotechnology Corporation, SmithKline Beecham will co-promote)
Argatroban, inj.
Indication: anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia.
Date approved: 30-06-2000

Angiomax® (The Medicines Company)
Bivalirudin, inj.
Indication: anticoagulant for concomitant use with aspirin in patients with unstable angina undergoing percutaneous transluminal angioplasty.
Date approved: 15-12-2000

Cetrotide® (Asta Medica)
Cetrorelix acetate 0.25 and 3 mg, inj.
Indication: ovarian stimulation agent for prevention of premature LH surges in women undergoing controlled ovarian stimulation.
Date approved: 11-08-2000 (available also in Italy)

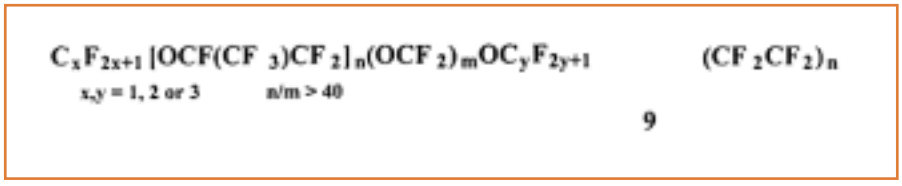

Figure 8

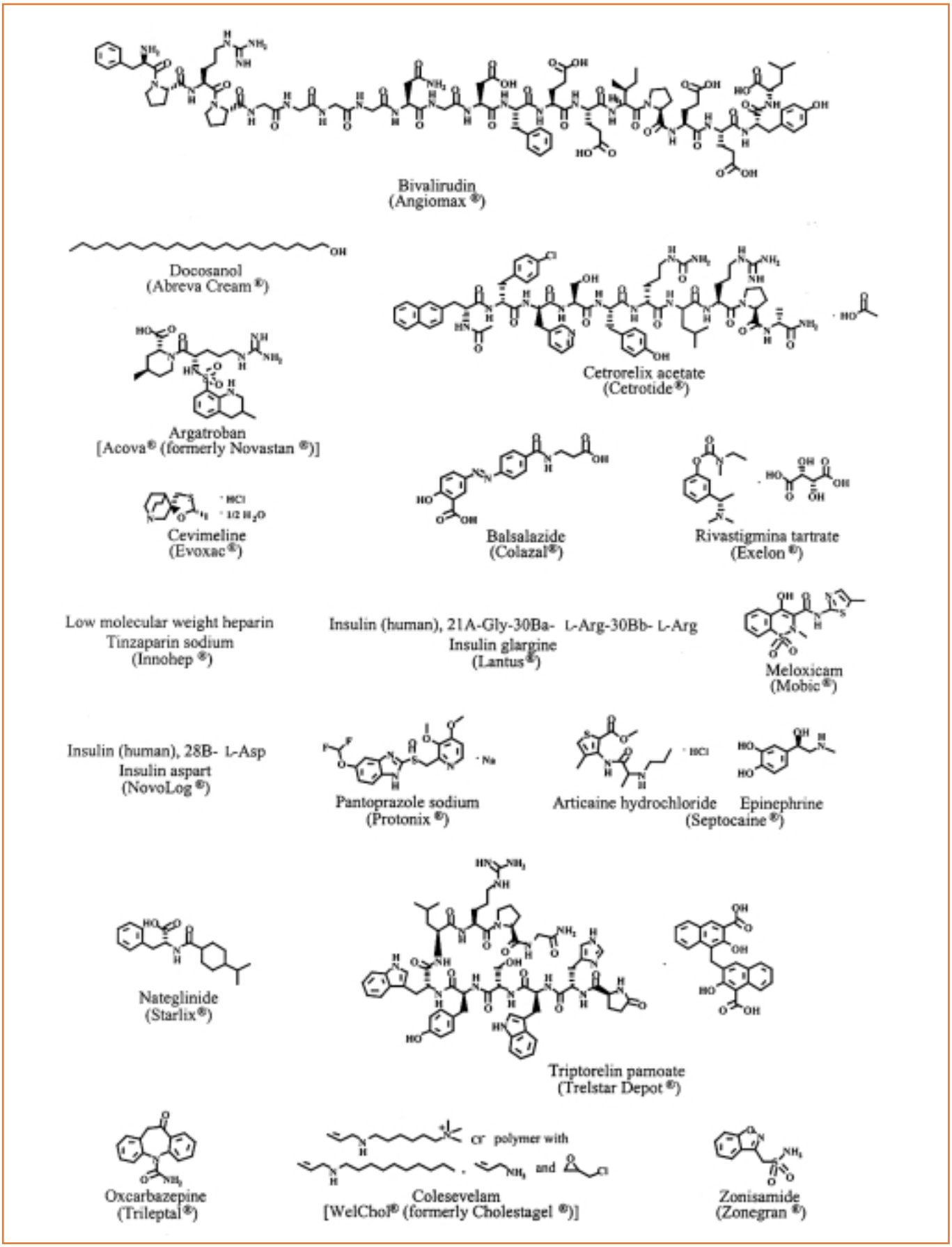
Bivalirudin
(Angiomax ®)
Docosanol
(Abreva Cream ®)
Cetrorelix acetate
(Cetrotide ®)
Argatroban
[Acova® (formerly Novastan ®)]
Cevimeline
(Evoxac ®)
Balsalazide
(Colazal®)
Rivastigmina tartrate
(Exelon ®)
Low molecular weight heparin
Tinzaparin sodium
(Innohep ®)
Insulin (human), 21A-Gly-30Ba- L-Arg-30Bb- L-Arg
Insulin glargine
(Lantus ®)
Meloxicam
(Mobic ®)
Insulin (human), 28B- L-Asp
Insulin aspart
(NovoLog ®)
Pantoprazole sodium
(Protonix ®)
Articaine hydrochloride
Epinephrine
(Septocaine ®)
Nateglinide
(Starlix ®)
Triptorelin pamoate
(Trelstar Depot ®)
Oxcarbazepine
(Trileptal ®)
polymer with
and
Colesevelam
[WelChol® (formerly Cholestagel ®)]
Zonisamide
(Zonegran ®)

Figure 9

Colazal® (Salix Pharmaceuticals)
Balsalazide disodium 750 mg, capsule
Indication: anti-inflammatory for treatment of mildly to moderately active ulcerative colitis.
Date approved: 18-07-2000

Evoxac® (SnowBrand Pharmaceuticals, Daiichi will promote)
Cevimeline hydrochloride hemihydrate 30 mg, capsule
Indication: cholinergic agonist for treatment of dry mouth symptoms in patients with Sjogren's syndrome.
Date approved: 11-01-2000

Exelon® (Novartis)
Rivastigmine tartrate 1.5, 3, 4.5 and 6 mg, capsule; 2 mg/mL oral solution
Indication: reversible cholinesterase inhibitor for treatment of mild to moderate dementia of the Alzheimer's type.
Date approved: 21-04-2000 (available also in Italy)

Innohep® (DuPont Pharmaceuticals, licensed from Leo)
Tinzaparin sodium, inj.
Indication: low molecular weight heparin for treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin.
Date approved: 14-07-2000 (available also in Italy)

Lantus® (Aventis Pharmaceuticals)
Insulin glargine, inj.
Indication: biosynthetic basal insulin for once-daily subcutaneous administration at bedtime in the treatment of adult and pediatric patients with type 2 diabetes mellitus for control of hyperglycemia.
Date approved: 20-04-2000

Mobic® (Boehringer Ingelheim Pharmaceuticals, Abbott Laboratories will co-promote)
Meloxicam 7.5 mg, tab.
Indication: NSAID for treatment of signs and symptoms of osteoarthritis.
Date approved: 14-04-2000 (available also in Italy)

NovoLog® (Novo Nordisk)
Insulin aspart, rNDA origin, inj.
Indication: rapid-acting insulin analog for treatment of adult patients with diabetes mellitus for control of hyperglycemia.
Date approved: 07-06-2000

Protonix® (Wyeth-Ayerst)
Pantoprazole sodium 40 mg, delayed-release tab.
Indication: proton pump inhibitor in tablet formulation for short-term treatment in the healing and symptomatic relief of erosive esophagitis.
Date approved: 02-02-2000

Septocaine® (Deproco)
Articaine hydrochloride 4%, epinephrine 1:100,000, solution for inj.
Indication: infiltration or nerve block anesthesia for use in dentistry.
Date approved: 03-04-2000

Starlix® (Novartis Pharmaceuticals)
Nateglinide 60 and 120 mg, tab.
Indication: D-phenylalanine derivative for use as monotherapy for type 2 diabetes and as a concomitant therapy to metformin.
Date approved: 22-12-2000

Trelstar Depot® (Pharmacia, licensed from Debio Recherche Pharmaceutique)
Triptorelin pamoate, inj.
Indication: synthetic luteinizing hormone-releasing hormone agonist for palliative treatment of advanced prostate cancer.
Date approved: 15-06-2000

Trileptal® (Novartis Pharmaceuticals)
Oxcarbazepine 150, 300 and 600 mg, tab.
Indication: anticonvulsant for treatment of partial seizures as adjunctive or monotherapy in adults and as adjunctive therapy in children aged 4 to 16.
Date approved: 14-01-2000

WelChol® (formerly *Cholestagel*®) (GelTex Pharmaceuticals, Inc.; Sankyo Parke Davis will market)
Colesevelam hydrochloride 375 mg, capsule; 625 mg, tab.
Indication: bile acid sequestrant/polymer-based lipid lowering agent for reduction of elevated LDL-cholesterol, alone or in combination with an HMG-CoA reductase inhibitor, in patients with primary hypercholesterolemia (Frederickson Type IIa).
Date approved: 26-05-2000

Zonegran® (Dainippon Pharmaceuticals, Elan Pharmaceuticals will market)
Zonisamide 100 mg, capsule
Indication: sulfonamide for adjunctive treatment of partial seizures in adults with epilepsy.
Date approved: 27-03-2000

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