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NEWLY FDA-APPROVED DRUGS AND BIOLOGICS (JANUARY-DECEMBER 2004). Part 1

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 1 only some of the drugs subjected to "Priority Review" (i.e., those representing significant improvements compared with marketed products [1]) and the BLA will be considered (7 NME and 5 BLA, 59 references). As for the other drugs subjected to "Priority Review" (10 NME) and those subject to "Standard Review" (i.e., those having therapeutic qualities similar to those of already marketed products [1]) (14 NME), information will be given in Part 2 [2]. This review follows the others about NME approved by the FDA in the years 1998-2003 [3].

New molecular entities and biological license applications approved in 2004 with priority review. Part 1

In order to offer an overview of the subject, the drugs have been grouped 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 1 anticancer drugs, enzymes and BLA are reported.

Anticancer drugs

Alimta® (Lilly) (orphan drug)
Pemetrexed disodium, 500 mg, lyophilized powder for intravenous (IV) infusion [5]
Indication: thymidylate synthase inhibitor for use in combination with cisplatin for the treatment of patients with malignant pleural mesothelioma (MPM) whose disease is either unresectable or who are otherwise not candidates for curative surgery.
Date approved: 04-02-2004

MPM is a rare but aggressive tumor that most often arises from mesothelial cells of the pleura and is associated frequently with asbestos exposure [6]. The prognosis for patients with MPM is poor and time of survival without treatment or after surgical resection is not long [6]. Treatment with radiation therapy has also been disappointing and limited by difficulties of irradiating disease tissue while avoiding toxicity. Various cytotoxic drugs, such as cisplatin, gemcitabine and methotrexate as single agent have demonstrated a poor response without improvement in overall survival [6].
Pemetrexed disodium (**1**, Fig. 2) is a pyrrolopyrimidine analogue of folic acid synthesized as reported in [7]. **1** was discovered through screening of derivatives of lometrexol, a glycinamide ribonucleotide formyltransferase (GARF) inhibitor known for its anticancer activity [7, 8]. After being transported into cells via the reduced folate carrier, which is involved in the uptake of physiological folates, **1** is metabolized by folylpolyglutamate synthase [8, 9]. These polyglutamated forms are potent inhibitors of TS and weak inhibitor of GARF and dihydrofolate reductase, all three folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides, and have an increased intracellular half-life resulted in prolonged drug action in malignant cells. This multi-targeted mechanism of action distinguishes **1** from other antifolate compounds [5c, 6-10]. The combination of **1** and cisplatin is the first chemotherapy regimen approved by the FDA for MPM treatment [5b] and offers a significant advantage in terms of response rate, survival and time to progression in patients with this disease [6]. Some months after the approval discussed here, **1** also received an accelerated approval in second-line treatment of non-small-cell lung cancer [11].

Tarceva™ (Genentech/OSI)
Erlotinib hydrochloride, 25, 100 & 150 mg, tablets [12]
Indication: epidermal growth factor receptor inhibition for treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen.
Date approved: 18-11-2004

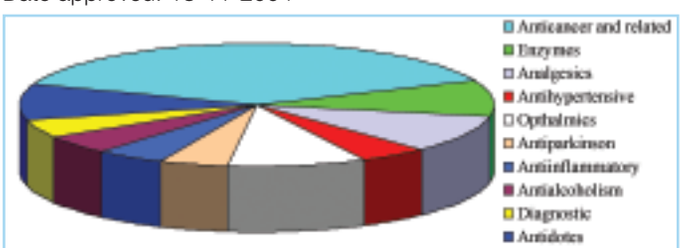

Fig. 1 - Therapeutic classes of NME and BLA approved by "priority review"

The growth of NSCLC, which accounts for over 80% of all malignant lung tumors, is regulated by various growth factors, acting through their respective transmembrane receptors, such as EGFR [13], which represents an ideal target for development of newly targeted therapies [14]. EGFR is a member of the ErbB family of tyrosine kinase receptors [14]. These receptors exist as inactive monomers: ligand binding determines a conformational change in the extracellular domain including receptor dimerization with consequent receptor activation, through a transphosphorylation of intracellular domain tyrosines [14a,b]. These phosphorylated tyrosines serve as the binding sites for several signal transducers and adaptor molecules, which initiate a cascade of biochemical events resulting in cell proliferation [14a]. The knowledge about EGFR led researchers to investigate several approaches to targeting this receptor including monoclonal antibodies directed against the extracellular domain such as cetuximab (see above) and small-molecule tyrosine kinase inhibitors such as gefinitib [15, 16, 3f].

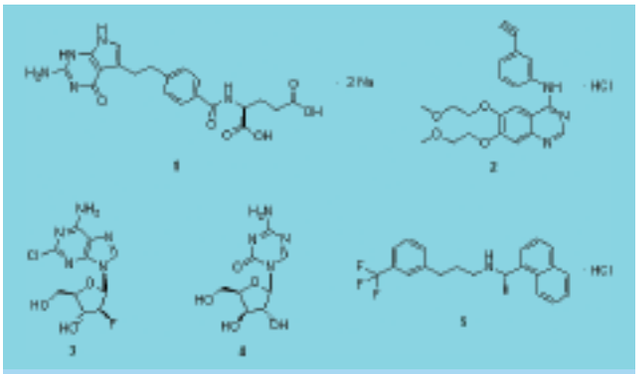

Fig. 2 - Anticancer drugs

Erlotinib hydrochloride (**2**, Fig. 2), a quinazoline derivative synthesized as described in [17], is a small molecule that competes with the binding of ATP to the intracellular tyrosine kinase domain of EGFR, thereby inhibiting receptor autophosphorylation and blocking downstream signal transduction [15, 12c, 18]. The evidence suggests that **2** may be a more efficient agent than gefinitib, a molecule which was approved last year as third line regimen [19]. Recently it was shown that some mutations in the EGFR tyrosine kinase domain are associated with response to **2** and gefinitib [20]. Disclosures about **2** and gefinitib are reported in [19, 20].

Clolar™ (Genzyme) (orphan drug)
Clofarabine, 20 mg, solution for IV infusion [21]
Indication: purine nucleoside analog for treatment of pediatric patients one to 21 years old with relapsed or refractory acute lymphoblastic leukemia (ALL) after at least two prior regimens.
Date approved: 28-12-2004 (accelerated approved)

ALL is one of the most common malignancies in children and adolescents [22]. Although the frequency of particular genetic subtypes differs in these categories of patients, the general mechanisms underlying the induction of ALL are similar [23]. This comprises genetic alterations that contribute to the leukemic transformation of hematopoietic stem cells or their committed progenitors by changing cellular functions [23]. They alter key regulatory processes by maintaining or enhancing an unlimited capacity for self-renewal, subverting the controls of normal proliferation, blocking differentiation and promoting resistance to death signals (apoptosis) [23]. Nucleoside analogues, such as cytarabine, are an important class of highly effective cytotoxic drugs for the treatment of ALL [22, 24]; cladribine and fludarabine have shown activity in ALL but at dose levels associated with prohibitive neurotoxicities [22, 24]. Clofarabine (**3**, Fig. 2) is a deoxyadenosine analogue synthesized as reported [25]. **3** was designed as a rational extension of the experience with cladribine and fludarabine resulting in a hybrid of these molecules in which a halogen in position 2 of the purine ring makes resistance to deamination and a fluorine moiety at the 2'-carbon in the arabino configuration of **3** increases stability in acid and resistance to cleavage of the glycosidic bond [22, 24, 25]. **3** acts after intracellular conversion by deoxycytidine kinase to the 5'-monophosphate metabolite, and then by conversion of mono- and diphosphokinases to the active 5-triphosphate form [22]. This derivative inhibits DNA synthesis by decreasing cellular deoxynucleotide triphosphate pools through an inhibitory action on ribonucleotide reductase, and by terminating DNA chain elongation and inhibiting repair through incorporation into the DNA chain by competitive inhibition of DNA polymerase [21b, 26].

Vidaza™ (Pharmion) (orphan drug)
Azacitidine, 100 mg, lyophilized powder for subcutaneous injection [27]
Indication: hypomethylating agent for treatment of refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts in trasformation (RAEB-T), and chronic myelomonocytic leukemia (CMcL).
Date approved: 19-05-2004

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal haematological disorders characterized by ineffective

haematopoiesis leading to blood cytopenias with generally hypercellular bone marrow and dysplasia of the cellular elements [27a]. MDS comprises various categories including RA, RARS, RAEB-T and CMcL [27a]. Standard treatment consists of supportive measures such as blood transfusions, erythropoietin for anemia and antibiotics to treat opportunistic infections [27b]. Combination chemotherapy regimens, such as cytarabine plus the anthracycline doxorubicin induce a complete response in a limited number of patients, for an average period of less than one year and without improving survival [27b]. At present, the primary potentially curative treatment is allogeneic stem-cell transplantation but such therapy is often not appropriate for MDS patients owing to their advanced age or accompanying diseases [28]. DNA methylation is a key "epigenetic" mechanism that contributs to cancer initiation and progression by inactivation of the expression of genes that are essential for the control of normal cell growth, differentiation and apoptosis; since hypermethylation is involved in MDS, recent treatment strategies address this phenomenon [27a, 28a, 29].
Azacitidine (**4**, Fig. 2) is a pyrimidine nucleoside (cytidine) analogue synthesized as described in [30]. **4**, after incorporation into DNA, acts by noncompetitively inhibiting DNA methyltransferase [27a] causing hypomethylation of DNA and consequent reactivation of previously silenced genes, including tumour-suppressor genes; in addition, it is thought that **4** exerts its neoplastic effects also through incorporation into RNA, as well as direct cytotoxicity [28a, 27c, 29a]. **4** improves the quality of life for patients with MDS and probably prolongs their survival [27b].

Sensipar™ (Amgen) (orphan drug)
Cinacalcet hydrochloride, 30, 60 & 90 mg, tablet [31]
Indication: oral calcimimetic agent for treatment of secondary hyperparathyroidism (HPT) in patients with chronic kidney disease on dialysis and treatment of hypercalcemia in patients with parathyroid carcinoma.
Date approved: 08-03-2004

Secondary HPT is a frequent complication associated with chronic kidney disease, elevated parathyroid hormone (PTH) levels, decreased levels of 1,25-dihydroxyvitamin D and abnormalities in bone mineral metabolism that usually determine high levels of calcium and phosphorus in serum [31a,b]. Excessive secretion of PTH and high concentrations of calcium serum play an important role in various pathologies including parathyroid carcinoma [31a,b]. Traditional therapies for secondary HPT, namely calcium-containing phosphate binders and vitamin D sterols, may contribute to hypercalcemia and/or hyperphosphataemia [31a, 32]. Management of parathyroid carcinoma foresees surgical resection but the carcinoma tends to recur within three years of chemotherapy and radiation therapy that often yield poor results [31, 33]. Calcimimetics are a new class of compounds: the first generation calcimimetic was R-568 which was discontinued because of poor bioavailability and the high variability of pharmacokinetics between patients [31c, 34].
Cinacalcet hydrochloride (**5**, Fig. 2), a phenylalkylamine derivative synthesized as reported in [35], reduces PTH levels by acting as positive allosteric modulator of the calcium-sensing receptor (CaR) through binding to the transmembrane region of the receptor inducing conformational changes that increase the receptor's sensitivity to calcium [36]. **5** constitutes a second generation CaR compounds and exhibits properties similar to R-568 but it possessed a higher bioavailabilty after oral administration and more consistent interpatient pharmacokinetics [31c]. Compared with other therapies for secondary HPT, **5** offers the advantage of lowering plasma PTH concentrations as well as those of serum calcium and phosphorus [37].

Enzymes

Amphadase™ (Amphastar)
Bovine hyaluronidase, USP 150 IU/mL, solution for injection [38a]
Date approved: 26-10-2004

Vitrase® (Ista)
Ovine hyaluronidase, USP 6200 IU/mL, solution for injection [38b]
Date approved: 05-05-2004

Indications: purified bovine/ovine protein enzyme for use as an adjuvant to increase absorption and dispersion of other injected drugs; for hyperdermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

Hyaluronidase is a spreading or diffusing substance which modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid, a polysaccharide found in the intracellular ground substance of connective tissue, and of certain specialized tissue [38]. Hyaluronidase acts by splitting the glucosaminidic bond between C1 of the glucosamine moiety and C4 of glucuronic acid. This temporarily decreases the viscosity of the cellular cement and promotes diffusion of injected fluids or of localized transudates or exudates, thus facilitating their absorption [38]. Bovine and ovine hyaluronidase (**6** and **7**, respectively) are preparations of purified testicular derivation, whose presence causes rapid spreading and provides local interstitial pressure adequate to furnish the neces-

sary mechanical impulse [38]. **6** and **7**, differing also by formulation in addition to source material [38], were formulated after the shortage created in 2002 succesively to Wyeth's Widase, a bovine hyaluronidase discontinued because of manufacturing problems [39]. More recently Vitrase® was also approved for treatment of vitreous hemorrhage [40].

New Biological License Applications Approved in 2004

Avastin™ (Genentech)
Bevacizumab, 100 & 400 mg, lyophilized powder for IV infusion [41]
Indication: vascular endothelial growth factor (VEGF) inhibitor for first-line treatment of metastatic colorectal cancer (CC) in combination with chemotherapy.
Date Approved: 26-02-2004 (priority review)

Erbitux™ (Bristol-Myers Squibb/ImClone)
Cetuximab 100 mg, lyophilized powder for IV infusion [42]
Indication: epidermal growth factor receptor (EGFR) antagonist for use in combination with irinotecan for the treatment of EGFR-expressing, metastatic colorectal cancer (CC) in patients refractory to irinotecan and for use as monotherapy in patients intolerant to irinotecan-based chemotherapy.
Date Approved: 12-02-2004 (priority review)

CC is a pathology comprising about 10% of cases of cancer. The initial treatment is surgical but the disease often recurs [42a]. Chemotherapy is indicated for patients in advanced disease; the therapeutic aim is to prolong survival, control symptoms and maintain or improve quality of life [42a]. Flurouracil, administered systematically with or without folinic acid, constituted the basis of first-line treatment regimens for several decades [42a]. More recently, the new chemotherapic agents, such as irinotecan and oxiplatin, that have become available, have increased response rates, time to disease progression and survival in patients with metastatic CC [42a].
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 disease, such as cancer [43]. There is evidence that tumor angiogenesis can be mediated by diffusible factors [43, 44]: vascular endothelial growth factor (VEGF) is a potent stimulator activating receptor tyrosine kinases on the surface of endothelial cells and is a key regulator of normal and pathological blood vessel growth [43, 44].
Bevacizumab (**8**) is a recombinant humanized monoclonal antibody that binds VEGF and prevents it from interaction with its receptor on endothelial cells, inhibiting formation of new blood vessels [41b,c, 44, 45].
An introduction about EGFR is reported in this review for **2** [13-16].
Cetuximab (**9**) is a recombinant, human/mouse chimeric monoclonal antibody that binds selectively to human EGFR and blocks phosphorylation and activation of receptor-associated kinase, resulting in inhibition of cell growth, induction of apoptosis, decreased matrix metalloproteinase and vascular endothelial growth factor production [42c,d, 46].

Stamp commemorating the Food and Drug Act of 1906, the first comprehensive federal law prohibiting the interstate commerce of adulterated or mislabelled foods and drugs [4]

For treatment of patients with advanced disease, a key issue is how to optimize the use of targeted agents, including **8** and **9** and those under investigation [47]. A recent study suggests that therapy with an antibody to VEGF and an antibody to EGFR can result in tumour shrinkage and meaningful benefit in many patients, and that this effect is augmented by addition of irinotecan [47]. These data raise the possibility that combined biological therapies, such as **8** plus **9** might become a viable strategy for the management of advanced disease without chemotherapy [47].

Kepivance™ (Amgen)
Palifermin, 6.25 mg, lyophilized powder for IV infusion [48]
Indication: recombinant human keratinocyte growth factor to decrease the incidence and duration of severe oral mucositis (OM) in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support.
Date Approved: 15-12-2004 (priority review)

OM, resulting from interactive biological phenomena taking place in both the epithelium and the submucosa, is a common adverse effect of myeloablative cancer therapy, affecting particular patients receiving high-dose chemotherapy with or without total-body irradiation for haematopoietic stem cell support [48a, 49]. Different strategies, such as oral-care protocols, cryotherapy and topical anti-infective or anti-inflammatory agents, coupled with palliative treatment (e.g. analgesics), are involved in the management of OM [48a, 50]. In addition, low-level laser therapy may reduce the incidence of OM and associated pain but expensive equipment and

specialized training are required for this therapy [48a, 50]. In the last few years, more detailed investigation of the mechanism involved in OM and the consideration that keratinocyte growth factor (KGF), a member of the heparin-binding family of fibroblast growth factors, is a potent and specific mitogen for different types of epithelial cells and protect these cells from various insults, led to consideration of KGF in the treatment of OM [48, 51].
Palifermin (**10**) is a more stable, *N*-terminal truncated version of KGF produced using recombinant DNA technology in *Escherichia coli*. **10** presents similar biological activity to the endogenous KGF and plays an important role in the repair of damaged epithelial tissues [48, 52]. In addition, the activation of specific transcription factors to upregulate detoxifying enzymes and attenuate proinflammatory cytokine production, the cytoprotective activities relating to DNA strand breaks and inhibition of apoptosis contribute to its efficacy against OM [53].

Tysabri® (formerly *Antegren*) (Biogen Idec/Elan)
Natalizumab, 300 mg, concentrate for IV infusion [54]
Indication: selective adhesion molecule inhibitor (alpha-4 antagonist) for treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations.
Date Approved: 23-11-2004 (priority review) (accelerated approval) (withdrawn from market 28-02-2005)

MS is the most common chronic inflammatory disorder of the central nervous system (CNS); despite this, the mechanisms of tissue damage and recovery in MS are not yet understood, even if it seems that at least two are dominant: inflammation with demyelination and axonal degeneration [55]. Corticosteroids, interferons and glatiramer acetate have been used in MS therapies but these drugs have a number of limitations. In recent years, since it was discovered that in both experimental autoimmune encephalomyelitis (EAE) and MS the formation of lesions is caused by entry of leukocytes into CNS cells by first adhering to inflamed brain endothelium, the efforts of researchers have been directed to $\alpha 4\beta 1$, the integrin identified as the key molecule in the adhesion process involving EAE cells [55, 56].
Natalizumab (**11**) is a recombinant humanized monoclonal antibody that binds to the $\alpha 4\beta 1$ subunit and has shown promising results in small-scale clinical trials in patients with MS [55, 57]. The indication of approval of **11** was based on results achieved after approximatively one year of treatment in ongoing controlled trials of two years of duration so the safety and efficacy of **11** were unknown [55, 54b]. On February 28, 2005, Biogen Idec and Elan decided to withdraw Tysabri® from the market because fatal progressive multifocal leukoencephalopathy was reported in two patients who received **11** during clinical trials [58]. On September 26, 2005 Biogen Idec and Elan announced that they are requesting a priority review for a new submission of Tysabri® for MS use [59].

NeutroSpec™ (formerly *Leu tech*) (Palatin)
Fanolesomab, kit for preparation of technetium (99m Tc) fanolesomab
Indication: radiodiagnostic murine IgM monoclonal antibody labeled with technetium Tc 99m for use in scintigraphic imaging of patients with equivocal signs and symptoms of appendicitis who are five years of age or older.
Date Approved: 02-07-2004 (standard review)

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