

Major New Drugs of 2008

Part 2

Author:
Marsha K. Millonig, MBA, RPh
President/CEO
Catalyst Enterprises, LLC

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Universal Program Numbers:

406-000-09-006-H01P & 406-000-09-006-H01T

The expiration date for this program is 1/31/10.



Learning Objectives:

Pharmacists:

After completing this lesson, for each new drug described the pharmacist should be able to:

1. List the brand and generic name, and manufacturer/distributor
2. Explain the agent's major therapeutic use(s)
3. Outline the drug's mechanism of action
4. Describe the pharmacokinetic profile and common drug-interactions
5. Discuss adverse effects and contraindications
6. Describe the dosage schedule, route of administration, strengths, and any storage issues
7. Outline monitoring parameters

Pharmacy Technicians:

After completing this lesson, for each new drug described the pharmacy technician should be able to:

- List the brand and generic name, and manufacturer/distributor
- Explain the agent's major therapeutic use(s)
- Describe the dosage schedule, route of administration, strengths, and any storage issues
- Outline monitoring parameters

In 2008, the Food and Drug Administration's (FDA) approval of new drugs was greater than the rate of approval the previous year and included more specialty/biologic medicines. The FDA approved 34 new molecular entities (NMEs) and biologic license applications (BLAs) for new entities, vaccines, imaging agents, and wound care. This CE program will provide pharmacists and pharmacy technicians with knowledge on the majority of new molecular entities approved by the FDA in 2008. Some diagnostic, anesthesia, and wound care agents will not be discussed but will be included in the summary listing.

Toviaz (Fesoterodine, Pfizer)

Toviaz is a muscarinic receptor antagonist that is metabolized to its active metabolite, 5-hydroxymethyl tolterodine, for treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. Muscarinic receptors play a role in contractions of urinary bladder smooth muscle and stimulation of salivary secretion. Inhibition of these receptors in the bladder is presumed to be the mechanism by which fesoterodine produces its effects.

Hepatic metabolism and renal excretion contribute significantly to the elimination of the active metabolite. The drug's half-life after oral administration is four hours. Because of its hepatic metabolism, doses of Toviaz greater than 4mg are not recommended in patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole and clarithromycin.

In clinical studies, the most frequent adverse events were: dry mouth and constipation. Toviaz is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients with known hypersensitivity to the drug or its ingredients. Toviaz should be used with caution in patients with clinically significant bladder outlet obstruction, decreased gastrointestinal motility, controlled narrow-angle glaucoma, and significantly reduced hepatic or renal function. The drug is not recommended for use in patients with severe hepatic impairment.

Toviaz is available as 4 mg and 8 mg extended release tablets in bottles of 30 and 90 tablets. The product is stored at 68° to 77°F.

Treanda (Bendamustine, Cephalon)

Treanda is a purine analogue/alkylator hybrid for the treatment of chronic lymphocytic leukemia and indolent B-cell non-Hodgkin's lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. Though the drug's exact mechanism of action remains unknown, it may act in two distinct ways to kill cancer cells. Preclinical studies suggest that it may lead to cell death by a process known as apoptosis (programmed cell death) as well as by an alternate cell death pathway which disrupts normal cell division known as mitotic catastrophe (a non-apoptotic pathway).

Concomitant CYP1A2 inducers or inhibitors (e.g. Cipor, Luvox) have the potential to affect the exposure of Treanda because the drug is metabolized by the CYP1A2 pathway to

two active metabolites. About 90% of the drug is eliminated in the feces.

The most common non-hematologic adverse reactions are nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decrease, dyspnea, rash and stomatitis. The most common hematologic abnormalities are lymphopenia, leukopenia, anemia, thrombocytopenia and neutropenia. The drug should not be used in patients with renal impairment if their CrCL is <40 mL/min or with moderate to severe hepatic impairment.

For CLL, Treanda's dosage is 100 mg/m² infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. The recommended dose for indolent NHL is 120 mg/m² administered on days one and two of a 21-day cycle, for up to eight cycles. Treanda is supplied in individual cartons of 20 mL amber single-use vials containing 100 mg of bendamustine hydrochloride as a white to off-white lyophilized powder. It is stored at 77°F.

Vimpat (Lacosamide, Schwarz)

Vimpat is a functionalized amino acid that enhances slow activation of voltage-gated sodium channels for oral adjunctive therapy of partial onset seizures in patients with epilepsy who are 17 years and older. It is also given by short-term injection when oral therapy is not feasible.

The drug is metabolized by the liver and excreted primarily in the urine. Peak plasma concentrations are achieved between 1 to 4 hours after oral administration.

The most common adverse reactions experienced with Vimpat are dizziness, headache, nausea, and diplopia. While there are no contraindications list in the labeling, caution is advised for patients with known cardiac conduction problems, who are taking drugs known to induce PR interval prolongation, or with severe cardiac disease such as myocardial ischemia or heart failure.

Vimpat is given 50 mg twice daily (100 mg/day). The dose may be increased, based on clinical response and tolerability, at weekly intervals by 100 mg/day given as two divided doses to a daily dose of 200 to 400 mg/day. Vimpat injection may be given without further dilution or mixed in compatible diluent and should be administered intravenously over a period of 30 to 60 minutes. The drug is supplied as 50, 100, 150, and 200 mg tablets in bottles of 60 and 180 tablets, and a 200 mg/20 mL single-use vial. Storage is at controlled room temperature.

Xenazine (Tetrabenazine, Prestwick)

Xenazine is the first medication to specifically treat chorea, the jerky body movements associated with Huntington's Disease. Xenazine's precise mechanism of action is unknown but is believed to be a reversible depletor of monoamines (dopamine, serotonin, norepinephrine, and histamine) from nerve terminals by inhibiting a molecule known as VMAT2 (vesicular monoamine transporter).

The results of *in vitro* studies do not suggest that Xenazine or its metabolites are likely to result in clinically significant inhibition of CYP2D6, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A. Their effect on CYP2B6 has not been evaluated. Patients taking medications

that suppress CYP2D6 should take half the normal dosage of Xenazine. Based on *in vitro* studies, there is a clinically significant interaction between Xenazine and other P450 inhibitors. Xenazine's approval includes a black-box warning and required medication guide that warns of the potential for serious risks associated with depression and suicidal thoughts and actions as seen in clinical trials.

The most common side effects associated with Xenazine are sedation/somnolence, fatigue, insomnia, depression, akathisia, and nausea. The drug is contraindicated in patients who are actively suicidal, with untreated or inadequately treated depression, with impaired hepatic function, and taking monoamine oxidase inhibitors. Xenazine is contraindicated in patients taking reserpine. At least 20 days should elapse after stopping reserpine before starting the drug.

Xenazine is an orally-administered tablet with dosages individualized for each patient. Dosages are titrated beginning with 12.5 mg administered once in the morning. Then, after a week of therapy, the dosage may be adjusted to 25 mg administered as 12.5 mg twice daily. Dosages should be adjusted by 12.5 mg per week to a maximum of 50 mg per day until chorea is well controlled and severe adverse effects do not occur. The maximum single daily dosage should be 25 mg per day. Dosages between 37.5 to 50 mg should be administered 3 times per day.

Xenazine is available as 12.5 mg and 25 mg tablets in bottles of 112 that should be stored at room temperature.

Biologicals Approved in 2008

Arcalyst (Rilonacept, Regeneron)

Arcalyst, an orphan drug, is an interleukin-1 blocker for the long-term treatment of Cryopyrin-Assisted Periodic Syndromes, including Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome. FCAS is a rare, inherited inflammatory disorder characterized by frequent, recurrent episodes of rash, fever/chills, joint pain, fatigue, eye pain/redness, and other signs/symptoms of systemic inflammation triggered by exposure to cooling temperatures. Onset of FCAS occurs during infancy and early childhood and persists throughout the patient's life. Muckle-Wells Syndrome is a rare autosomal dominant disease which causes sensorineural deafness, recurrent hives, and can lead to amyloidosis. Individuals with MWS often have episodic fever, chills, and painful joints. As a result, MWS is considered a type of periodic fever syndrome. MWS is caused by a defect in the CIAS1 gene which creates the protein cryopyrin.

The most frequent adverse events associated with Arcalyst include injection site reactions, and upper respiratory tract infections. No formal drug interaction studies have been conducted.

Interleukin -1 (IL-1) blockade may interfere with the immune response to infections. Treatment with another medication that works through inhibition of IL-1 has been associated with an increased risk of serious infections, and serious infections have been reported in patients taking the drug.

Arcalyst is given subcutaneously with a loading dose of 320 mg delivered as 2 ml injections on the same day but at separate injection sites. Treatment is continued on a weekly

basis with 160 mg as a single injection. Arcalyst is supplied in single-use vials containing 220 mg of the drug in lyophilized powder form for reconstitution. It is refrigerated.

Cimzia (Certolizumab, UCB)

Cimzia is a tumor-necrosis factor (TNF) blocker for reducing the signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderate to severely active disease who do not respond well to traditional therapy.

No specific contraindications are listed in the product labeling. However, live vaccines should not be given with Cimzia.

The most common side effects of Cimzia are upper respiratory infections, urinary tract infections, joint pain, and injection site reactions. The drug can lower the ability of the immune system to fight infections. Serious infections, including tuberculosis (TB) have happened in patients taking Cimzia. Physicians should test patients prior to treatment and monitor them carefully during treatment.

TNF blockers have also been associated with a risk of lymphomas. The FDA is conducting an ongoing safety review of TNF blockers.

The dosage of Cimzia is 400 mg subcutaneously initially, and at 2 and 4 weeks. If a patient responds, then 400 mg is given SC every 4 weeks. The drug is supplied as a 200 mg single use injection in a lyophilized powder for reconstitution. It is refrigerated.

Cinryze (C1-esterase inhibitor, Lev/Viro-Pharma)

Cinryze is a pasteurized, nanofiltered C1 inhibitor indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE). HAE is a genetic disorder caused by deficiency or dysfunction of the plasma protein C1 inhibitor. Cinryze is a biological agent that replaces the missing C1 protein inhibitor absent in patients with HAE. Without the use of Cinryze, patients with episodes of acute HAE receive fresh, frozen plasma to replace the missing C1 inhibitor.

The most common adverse reactions observed related to Cinryze treatment were sinusitis, rash, headache, and upper respiratory tract infection. In rare cases, there is a possibility of allergic reactions. Cinryze is made from human plasma. As such, it may contain infectious agents. The risk that such products will transmit an infectious agent has been reduced by screening donors, testing for the presence of infections, and by inactivating or removing a broad range of viruses during the manufacturing process.

Cinryze's typical dosing is 1,000 units administered intravenously for both short-term prophylaxis and acute attacks every 3 to 4 days. One unit is typically the equivalent of 1 ml of C1 inhibitor found in normal plasma. The drug is supplied as approximately 500 Units (lyophilized) in an 8 mL vial. To obtain the required dose, 2 vials are reconstituted with 2 vials Sterile Water for Injection, USP (5 mL each) using aseptic sterile technique. The drug should be administered at room temperature within 3 hours of reconstitution. Prior to reconstitution, the drug is stored between 36-77°F.

Nplate (Romiplostim SC inj, Amgen)

Nplate is a thrombopoietin receptor agonist for the treatment of thrombocytopenia in patients with chronic (idiopathic) thrombocytopenic purpura (ITP) who have not responded sufficiently to corticosteroids, immunoglobulins, or splenectomy. ITP is a chronic and potentially serious autoimmune disorder characterized by low platelet counts in the blood, a condition known as thrombocytopenia. With ITP, platelets are destroyed by the patient's own immune system.

In the long-term extension study in patients with ITP receiving weekly treatment of Nplate subcutaneously, the pharmacokinetics of romiplostim over the dose range of 3 to 15 mcg/kg indicated that peak serum concentrations of romiplostim were observed about 7 to 50 hours post dose (median: 14 hours) with half-life values ranging from 1 to 34 days (median: 3.5 days). No formal drug interaction studies have been conducted.

The most common adverse events reported in patients treated with Nplate were headache, fatigue, epistaxis, arthralgia, and contusion. There are no contraindications on the medication labeling.

This is adjusted weekly dose by increments of 1 mcg/kg to achieve and maintain a platelet count $\geq 50 \times 10^9/L$ as necessary to reduce the risk for bleeding. The maximum weekly dose is 10 mcg/kg. The drug is discontinued if platelet count does not increase after 4 weeks at the maximum dose.

The drug is supplied in strengths of 250 mcg or 500 mcg of deliverable romiplostim in single-use vials. It is stored refrigerated.

Recothrom (Thrombin, recombinant, ZymoGenetics)

Recothrom is a recombinant, plasma-free human thrombin for topical use as an aid to hemostasis.

Recothrom is the first thrombin approved by the FDA that is produced via recombinant DNA technology.

In clinical studies, the most common adverse event reported was incision site complication. No drug interaction studies have been conducted. It should be used with caution in patients with allergies to hamsters.

It is available as 5000-IU and 20,000-IU vials of sterile powder for solution. It is reconstituted to a solution containing 1000 IU/mL and is applied directly to bleeding site surface or in conjunction with absorbable gelatin sponge.

Rotarix (Rotavirus gastroenteritis, GSK)

Rotarix is a live vaccine for the prevention of rotavirus gastroenteritis caused by G1 types in infants and children. It is administered as a two-dose series between the ages of 6 to 24 weeks.

In two safety and efficacy studies, one to two months after a 2-dose series, 86.5% of 787 recipients of the vaccine seroconverted compared with 6.7% of 420 placebo recipients and 76.8% of 393 recipients of the vaccine seroconverted compared with 9.7% of 341 placebo recipients, respectively.

The vaccine is contraindicated in infants with a history of uncorrected congenital malformation of the gastrointestinal tract that would predispose the infant to intussusception. It should not be given to infants suffering from acute diarrhea or vomiting. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids, may reduce the immune response to Rotarix.

Rotarix is administered 1-ml orally to infants beginning at 6 weeks of age. A second dose is administered after an interval of at least 4 weeks and prior to 24 weeks of age. The drug is available as a vial of lyophilized vaccine, a prefilled oral applicator of liquid diluent (1 mL) with a plunger stopper, and a transfer adapter for reconstitution. It is stored in the refrigerator.

Xyntha (Moroctocog alfa, Wyeth)

Xyntha is a recombinant Factor VIII for control and prevention of bleeding, including surgical bleeding, in patients diagnosed with hemophilia A. Xyntha is manufactured using recombinant DNA techniques. There are no drug interactions or contraindications for the product.

The most common adverse reactions in clinical studies were headache and pyrexia. Allergic-type hypersensitivity reactions are possible. Patients should be informed of the early signs of hypersensitivity reactions, including hives (rash with itching), generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physicians if these symptoms occur. Patients should be advised to contact their physician or treatment facility for further treatment and/or assessment, if they experience a lack of a clinical response to factor VIII replacement therapy, as this may be a manifestation of an inhibitor.

Xyntha dosage is determined using the following formula: Required units = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL). The drug comes as a powder is available as 250, 500, 1000, or 2000 IU in single-use vials reconstituted and given IV.

Xyntha is stored in the refrigerator at 36° to 46°F (2° to 8°C), but can last at room temperature (below 77°F) for up to 3 months.

New Molecular Entities 2008

Brand Name	Generic Name	Sponsor	Indication	Route of Administration	Date Approved
AdreView	Lobenguane I 123	GE Healthcare	Diagnostic radionuclide for detection of primary/metastatic pheochromocytoma or neuroblastoma	IV	9/19/2008
Banzel	Rufinamide	Eisai	Lennox-Gastaut syndrome seizures	Oral	11/14/2008
Cleviprex	Clevidipine butyrate IV	The Medicines Company	IV Ca Channel blocker	IV	8/1/2008
Degarelix	Degarelix	Ferring	Advanced prostate cancer	Subcutaneous injection	12/24/2008
Durezol	Difluprednate ophthalmic emulsion	Sirion	Topical corticosteroid for inflammation/pain associated with ocular surgery	Eye drop	6/23/2008
Entereg	Alvimopan	Adolor/GSK	Accelerate bowel function in patients who have undergone partial large/small bowel resection	Oral	5/20/2008
Eovist	Gadoxetate, IV	Bayer	Diagnostic MRI of liver	IV	7/3/2008
Intelence	Etravirine	Tibotec	HIV	Oral	1/18/2008
Lexiscan	Regadenosan IV	CV Therapeutics/Astellas	Pharmacologic stress agent used in myocardial perfusion imaging	IV	4/10/2008
Lusedra	Fospropofol IV	Eisai	Sedative-hypnotic agent for monitored anesthesia	IV	12/12/2008
Mozobil	Plerixafor	Genzyme	Bone marrow transplant agent used with granulocyte-colony stimulating factor (G-CSF)	Subcutaneous injection	12/15/2008
Pristiq	Desvenlafaxine	Wyeth	Major depressive disorder	Oral	2/29/2008
Promacta	Eltrombopag	GSK	Thrombocytopenia	Oral	11/20/2008
Rapaflo	Silodosin	Watson	Benign prostatic hyperplasia	Oral	10/8/2008
Tapentadol	Tapentadol	Johnson & Johnson	Moderate to severe acute pain	Oral	11/20/2008
Relistor	Methylnaltrexone bromide	Progenics/Wyeth	Opioid-induced constipation	Injection	4/24/2008
Toviaz	Fesoterodine	Pfizer	Overactive Bladder	Oral	10/31/2008
Treanda	Bendamustine IV	Cephalon	Chronic lymphocytic leukemia	IV	03/20/2008
Vasovist	Gadofosveset	Epix	Evaluation of aortoiliac occlusive disease in peripheral vascular disease	IV	12/22/2008
Vimpat	Lacosamide	Schwarz	Partial onset seizures in epilepsy	IV	10/28/2008
Xenazine	Tetrabenazine	Prestwick	Chorea of Huntington's disease	Oral	08/15/2008

Adapted from the FDA (<http://www.fda.gov/cder/rdmt/InternetNDA08.pdf>), Pharmaceuticals Approvals Monthly December 2008, and PhRMA's New Drug Approvals 2008 <http://www.phrma.org/files/2008%20Approvals%20011209.pdf>

Biologicals and Vaccines Approved in 2008

Brand Name	Generic Name	Sponsor	Indication	Route of Administration	Date Approved
Afluria	Influenza virus vaccine	CSL Limited	Influenza immunization in adults 18 and over	IM	07/30/2008
Arcalyst	Rilonacept, inj.	Regeneron	Familial cold auto-inflammatory syndrome & Muckle-Wells Syndrome	Subcutaneous injection	2/27/2008
Artiss	Febrin sealant (human)	Baxter	Medical adhesive for adhering autologous skin grafts to surgically prepared wound beds in burn patients	Sealant	3/19/2008
Cimzia	Certolizumab pegol, inj	UCB	Crohn's disease	Injection	4/22/2008
Cinryze	C1-esterase inhibitor	Lev/Viro-Pharma	Hereditary angioedema	Injection	10/10/2008
Fluarix	Influenza virus vaccine	GSK	Influenza immunization in adults 18 and over	IM	08/05/2008
FluLaval	Influenza virus vaccine	ID Biomedical	Influenza immunization in adults 18 and over	IM	07/28/2008
FluMist	Influenza virus vaccine, live, intranasal	MedImmune Vaccines	Influenza immunization in individuals 2-49 years	Intranasal	07/25/2008
FluVirin	Influenza virus vaccine	Novartis	Influenza immunization in persons 4 years of age and older	IM	08/01/2008
FluZone	Influenza virus vaccine	Sanofi Pasteur	Influenza immunization in persons 6 months of age and older	IM	07/14/2008
Kinrix	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine	GSK	Active immunization against diphtheria, tetanus, and acellular pertussis and the 4 th dose in the inactivated poliovirus vaccine series in children 4-6 years	IM	06/24/2008
Nplate	Romiplostim	Amgen	Idiopathic thrombocytopenic purpura	Subcutaneous injection	08/22/2008
Pentacel	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine and Haemophilus B Conjugate (Tetanus Toxoid Conjugate)	Sanofi Pasteur	Active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease caused by Haemophilus influenzae for persons 6 weeks to 4 years.	IM	6/20/2008
Recothrom	Thrombin (recombinant)	ZymoGenetics	Hemostasis aid		1/17/2008
Rotarix	Rotavirus gastroenteritis	GSK	Prevention of rotavirus in infants/children ages 6-24 weeks	Oral	3/19/2008
Xyntha	Moroctocog alfa (Antihemophilic Factor recombinant)	Wyeth	Control of bleeding in hemophilia A	IV	02/21/2008

Adapted from the FDA (<http://www.fda.gov/cder/rdmt/InternetNDA08.pdf>), Pharmaceuticals Approvals Monthly December 2008, and PhRMA's New Drug Approvals 2008 <http://www.phrma.org/files/2008%20Approvals%20011209.pdf>