

Major New Drugs — 2006

Part 1

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Goals and Objectives

Goals:

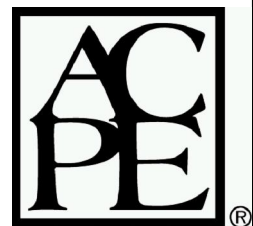
To provide the health care practitioner with knowledge on the new molecular entities approved by the Food and Drug Administration (FDA) in 2006.

Objectives:

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

1. List the generic and brand name, and manufacturer/distributor
2. Explain the agent's major therapeutic use(s)
3. Outline the 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

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Anidulafungin, injection (Eraxis — Pfizer Inc.)

Eraxis is an echinocandin antifungal for the treatment of patients with esophageal candidiasis and for the treatment of patients with candidemia and other forms of *Candida* infections (intraabdominal abscess and peritonitis). It is the third drug in this class approved by the FDA.

Eraxis is highly protein bound to albumin with extensive tissue distribution. Intravenous Eraxis has a half-life of 30-60 minutes. The drug does not undergo hepatic metabolism. Less than 1% of the drug is excreted in the urine while 30% of the dose is excreted in the feces.

The drug should not be used in patients who have experience hypersensitivity reactions to caspofungin (Cancidas) or micafungin (Mycamine). Significant hepatic dysfunction has occurred with the drug. Other adverse events include diarrhea, hypokalemia, ALT elevations, rash, dyspnea, and hypotension.

Eraxis is administered by IV infusion at a rate not exceeding 1.1mg/minute. For candidemia, the recommended dose is a single 200-mg loading dose followed by 100 mg IV each day for at least 14 days after the last positive culture. For esophageal candidiasis, the recommended dose is a single 100-mg loading dose followed by 50 mg everyday thereafter for at least 14 days after the last positive culture and 7 days after the last symptoms. Eraxis comes in 50 mg vials, in powder form for reconstitution with the resulting solution further diluted.

Avobenzone-2%, ecamsule-2%, and octocrylene-10% cream (Anthelios SX — L'Oréal)

Anthelios SX SPF 15, also known as Mexoryl SX, is a triple-combination moisturizing OTC cream for prevention of sunburn and to provide protection from UVA and UVB rays. Each sunscreen in incremental concentrations contributes to the UVA and UVB protection. The cream should not be used on severe burns, broken skin, or mucous membranes. Adverse events include dermatitis, dry skin, eczema, itching, and skin discomfort.

Biscalcitrates potassium/metronidazole/tetracycline (Pylera — Axcan)

Pylera is a combination treatment for *H.pylori* infection associated with duodenal ulcers. The drug is used in combination with a proton pump inhibitor to treat *H.Pylori*. Food significantly reduces the availability of each drug. This may be beneficial when local gastric effects are needed.

Metronidazole can inhibit alcohol metabolism so ethanol should not be ingested during therapy. Digoxin-stabilized patients should be monitored for toxicity. Metronidazole can also cause lithium and fluorouracil toxicity. Some antibiotics can interfere with the effectiveness of oral contraceptives, so patients should be advised to use additional forms of contraception while on therapy. Tetracyclines cause photosensitivity and may increase the photosensitizing effects of other drugs. Patients should be advised to use sunscreen and limit sun exposure while taking Pylera. Use of Mepron (atovaquone) should also be avoided.

Pylera is contraindicated in pregnancy. Adverse events include nausea, vomiting, diarrhea, and abdominal pain. Tongue discoloration may occur as well.

Pylera is an orally administered capsule containing 140 mg of biscalcitrates potassium, 125 mg of metronidazole, and 125 mg of tetracycline. The dosage is three capsules, four times a day, plus omeprazole 20 mg two times a day.

Ciclesonide nasal spray (Omnaris — Altana)

Omnaris is a glucocorticoid used in children and adults 12 years and older to treat nasal symptoms associated with seasonal and perennial allergic rhinitis.

Omnaris is an ester prodrug, requiring activation in the lung or other tissues to the active form which has 100-fold greater affinity for the glucocorticoid receptor than the parent compound. Both forms are highly protein bound. The active form is metabolized in the liver by cytochrome P450 3A4 and to a lesser extent by CYP2D6. Co-administration with ketoconazole should be avoided because it increased Omnaris bioavailability.

Patients with sensitivity to other corticosteroids should be cautious in using Omnaris. The drug can increase intraocular pressure in patients with glaucoma. It can exacerbate a number of viral, fungal, parasitic, and bacterial infections as well. Adverse events include epistaxis, nasopharyngitis, ear pain, and headache.

The recommended dose of Omnaris nasal spray is 200 mcg/day given as two sprays in each nostril once a day.

Darunavir

(Prezista — Johnson & Johnson)

Prezista is a protease inhibitor for use in combination with low-dose ritonavir (Norvir) and other antiretroviral agents for the treatment of HIV-1 infected adults whose infection has not responded to other antiretrovirals.

Prezista inhibits the HIV-1 protease and prevents formation of mature virus particles. The drug is a CYP3A inhibitor so it should not be co-administered with drugs primarily metabolized by CYP3A. The drug is metabolized in the liver.

Adverse events include severe skin rash, Stevens-Johnson syndrome, and fever. It should be used with caution in patients with sulfonamide allergy.

Prezista is available as an orally self-administered 300-mg tablet that is doses two tablets with 100 mg Norvir twice a day. It should be taken with food.

Dasatinib

(Sprycel — Bristol-Myers Squibb)

Sprycel is a multi-targeted kinase inhibitor for the treatment of chronic myelogenous leukemia in chronic, accelerated, or blast phases, as well as Philadelphia chromosome positive acute lymphoblastic leukemia that is resistant or intolerant to imatinib therapy.

Sprycel was specifically designed to inhibit SRC tyrosine kinase. The drug is extensively distributed in intravascular space with a three-to-five hour half-life. It is extensively metabolized by cytochrome P450 3A4 and it is a weak time-dependent CYP3A4 inhibitor.

Sprycel may cause myelosuppression, so complete blood counts should be performed weekly for the

first 2 months then monthly. Other adverse events include hemorrhage, QT prolongation, fluid retention, diarrhea, nausea, vomiting, abdominal pain, pyrexia, pneumonia, dyspnea, and cardiac failure. The drug should not be used with proton pump inhibitors or H₂-receptor antagonists.

Sprycel is available as an orally administered tablet in 20, 50, and 70 mg strengths. The recommended dosage is 70 mg twice daily in the morning and evening.

Decitabine injection

(Dacogen — MGI/SuperGen)

Dacogen is indicated for the treatment of patient with myelodysplastic syndrome (MDS) and secondary MDS of all French-American-British types. The drug improves overall response rate in combination with best supportive care.

Dacogen is an analog of a natural nucleoside that is thought to cause hypomethylation in neoplastic cells that may restore normal function to genes that are critical for controlling cellular differentiation.

Dacogen's metabolism and route of elimination is unknown but it is thought to be unlikely to inhibit or induce cytochrome P450 enzymes. Adverse events include neutropenia, thrombocytopenia, anemia, fatigue, pyrexia, nausea, constipation, diarrhea, cough, petechiae, and hyperglycemia.

Dacogen is administered via IV infusion over three hours. The usual dose is 15mg/m² every eight hours for three days with the treatment cycle repeated every six weeks. The product is supplied as a powder for reconstitution in 50 mg vials and the resultant solution must be further diluted.

Kunecatechins ointment

(Veregen — MediGene)

Veregen is a topical ointment used to treat external genital warts and reduce the severity and duration of symptoms.

The drug is the partially purified fraction of the water extract of green tea leaves and is a mixture of catechins and other tea components. The pharmacokinetics of topically applied Veregen are unknown.

The use of Veregen on open wounds should be avoided. Its efficacy has not been proven in immunosuppressed patients or for use longer than 16 weeks or in multiple treatment cycles. Adverse events are local, primarily application site reactions.

A 0.5 cm strand dose of Veregen is applied three times daily to all external genital and perianal warts until wart clearance occurs, but not longer than 16 weeks.

Lubiprostone (Amitiza — Sucampo/Takeda)

Amitiza is a prostaglandin metabolite used for the treatment of chronic idiopathic constipation in adults. The drug is a locally acting chloride channel activator that increases intestinal fluid secretion and intestinal motility.

Because of its local action, there is low potential for drug interactions. Amitiza is contraindicated in patients with a history of mechanical GI obstruction. Adverse events include nausea, diarrhea, and headache. The drug's safety in pregnancy has not been established.

Amitiza is an orally administered capsule with a recommended dose of 24 mcg taken two times a day with food.

Paliperidone (Invega — Johnson & Johnson)

Invega is an extended release dual dopamine D2/serotonin 5-HT₂ receptor antagonist for the treatment of schizophrenia. The drug is an active metabolite of risperidone (Risperdal).

Peak plasma concentrations of Invega are reached in about 24 hours with steady-state concentration achieved in 4-5 days. A high-fat or high-calorie meal increases the drug's concentration. The drug is highly protein bound (74%). While the drug is metabolized by the cytochrome P450 isoenzymes, no difference in the clearance or exposure in fast/slow metabolizers was found. The drug has an elimination half-life of 23 hours.

Invega should be used with caution in combination with other CNS depressants or drugs that can prolong the QTc interval. Additive hypotensive effects are seen with other CNS depressants.

Adverse events include headache, akathisia, extrapyramidal disorder, sedation, insomnia, agitation, anxiety, tachycardia, and sinus tachycardia.

Invega is supplied as a 6 mg oral capsule with a recommended dosage of 6 mg daily in the morning, with a maximum daily dose of 12 mg.

Posaconazole (Noxafil — Schering-Plough)

Noxafil is a broad-spectrum oral triazole antifungal agent more potent than itraconazole (Sporanox). The drug is indicated for the prophylaxis of invasive *Aspergillus* and *Candida* infections in patients 13 years and older who are at high risk for these infections due to being immunocompromised. It is also indicated in the treatment of oropharyngeal candidiasis refractory to itraconazole and/or fluconazole.

Adverse events include nausea, vomiting, diarrhea, and liver reactions. The drug may prolong the QT interval and concurrent use with other drugs that prolong the QT interval is contraindicated. Noxafil inhibits CYP3A4 and caution must be used when it is used with other CYP3A4 substrates and use of ergot derivatives is contraindicated.

Noxafil is an orally administered 40 mg/ml suspension that is administered with meals at a usual dose of 200 mg three times daily for prophylaxis. For treatment, a loading dose of 100 mg twice a day on the first day is followed by 100 mg once daily for 13 days. For the treatment of oral candidiasis the dose is 400 mg twice a day.

Ranolazine (Ranexa — CV Therapeutics)

Ranexa is a late sodium current inhibitor that exhibits antianginal activity and is used for the treatment of chronic angina.

Because Ranexa prolongs the QT interval, it should be reserved for patients who have not achieved an adequate response with other anti-anginal drugs. The drug is contraindicated in patients with pre-existing QT prolongation, who are taking other drugs that prolong the QT interval, who are being treated with a potent or moderately potent CYP3A

inhibitor, or in patients with liver disease. Adverse events include dizziness, headache, constipation, and nausea.

Ranexa is available as an orally administered 500 mg extended-release tablet with a recommended dose of 500 mg twice daily, not to exceed 1000 mg twice daily.

Rasagiline (Azilect — Teva)

Azilect is a second-generation MAO-B inhibitor for use as initial monotherapy in early Parkinson's disease patients and as adjunct therapy to levodopa in moderate-to-advanced stages.

Concurrent use with other MAO inhibitors or meperidine is contraindicated. Use of Azilect should be discontinued 14 days before starting treatment with these agents. Concurrent use of sympathomimetic amine, tramadol, methadone, propoxyphene, dextromethorphan, cyclobenzaprine, mirtazapine, or St. John's wort is contraindicated. Use of tricyclic, SSRI, or SNRI antidepressant should be avoided. The drug should not be used in patients with liver failure. Use of tyramine-rich foods should be restricted.

Patients should be advised to monitor for melanoma.

Adverse events may include flu syndrome, arthralgia, depression, dyspepsia, falls, and hallucinations.

Azilect is available as an oral self-administered 0.5 mg and 1 mg tablet. The usual dose is 1 mg daily as monotherapy and 0.5 mg daily as adjunct to levodopa.

Sitagliptin (Januvia — Merck)

Januvia is a dipeptidyl peptidase-4 (DPP-4) inhibitor that slows the inactivation of incretins, increases insulin release, and decreases glucagon concentration in circulation. Januvia is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. It is also indicated for use in combination with metformin or a thiazolidinedione in patients in whom a single agent does not provide adequate

glycemic control. Januvia should not be used in patients with type 1 diabetes mellitus or in the treatment of diabetic ketoacidosis.

Januvia is excreted primarily unchanged in the urine and the dose should be adjusted in patients with renal compromise. Adverse events include upper respiratory tract infection, nasopharyngitis, and headache. Minor increases in digoxin plasma concentrations have been seen so patients taking both agents should be monitored.

Januvia is an orally administered tablet available in 25 mg, 50 mg, and 100 mg tablets. The usual dosage is 100 mg once daily.

Sunitinib (Sutent — Pfizer, Inc.)

Sutent is a multi-targeted kinase inhibitor for the treatment of GI stromal tumors after disease progression and for advanced renal cell carcinoma. It is indicated for patients who fail on or cannot tolerate imatinib (Gleevec) therapy.

Sutent is metabolized by CYP3A4, therefore clinical important drug interactions may occur. The drug's action may be increased by strong CYP3A4 inhibitors (eg, clarithromycin, itraconazole, HIV protease inhibitors) and decreased by CYP3A4 inducers (eg, carbamazepine, rifampin, St. John's wort).

Adverse events include possible left ventricular dysfunction, hypertension, hemorrhagic events, fatigue, diarrhea, abdominal pain, nausea, vomiting, neutropenia, lymphopenia, thrombocytopenia, anemia, AST/ALT elevation. Sutent may harm the fetus so women of childbearing potential should be advised not to become pregnant.

Sutent is an orally administered capsule in 12.5 mg, 25 mg, and 50 mg strengths. The usual dosage is 50 mg once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off treatment.

Telbivudine (Tyzeka — Novartis/Idenix)

Tyzeka is an oral, once daily nucleoside analog for treatment of chronic hepatitis B in patients with evidence of viral replication and active liver inflammation.

Tyzeka is not a substrate or inhibitor of the CYP450 enzyme system. The drug is eliminated primarily by urine secretion of the active drug, so dose adjustments may be needed in patients with renal disease or impairment.

Adverse events include upper respiratory tract infections, malaise, abdominal pain, nasopharyngitis, headache, increased serum creatine phosphokinase (CPK), and myopathy. Patients should be advised to promptly report any unexplained muscle aches, pain, tenderness, or weakness.

Tyzeka is available as a 600 mg tablet with the recommended dose of 600 mg once daily.

Adverse effects include possible deep vein thrombosis, pulmonary embolism, anemia, thrombocytopenia, hyperglycemia, and QT prolongation. As such, blood cell counts should be performed every two weeks during the first two months of therapy, and monthly thereafter. Additionally, ECGs should be performed during each treatment. Other adverse events include GI reactions, taste disorders, fatigue, and chills.

Concomitant use of Zolinza with anticoagulants may increase the risk of bleeding. Concurrent use with valproic acid may increase the risk of toxicity.

Zolinza is available as an orally administered 100-mg capsule. The recommended dosage is 400 mg once daily with food.

Varenicline (Chantix — Pfizer, Inc.)

Chantix is a selective nicotinic acetylcholine receptor partial agonist for use as an aid to smoking cessation treatment. Chantix provides an agonist action that eases nicotine withdrawal symptoms and prevents binding of nicotine to receptors, thus reducing the satisfaction if an individual resumes smoking.

The drug is very well absorbed and after oral administration the systemic availability is high. Over 90% of the dose is eliminated unchanged in the urine.

Adverse events include nausea, insomnia, and abnormal dreams.

Individuals should set a quit smoking date and initiate treatment one week prior to the date. Chantix should be taken after eating with a full glass of water. The recommended dosage is 0.5 mg daily on days 1-3, 0.5 mg twice daily on days 4-7, then 1 mg twice daily on day 8 until the end of the 12-week course of therapy. Chantix is available as 0.5 mg and 1 mg orally administered tablets.

Vorinostat (Zolinza — Merck)

Zolinza is a histone deacetylase inhibitor for the treatment of advanced cutaneous T-cell lymphoma (progressive, persistent, or recurrent disease on or following two systemic therapies.)

New Molecular Entities 2006 (Not Biologics)

Generic Name	Brand Name	Manufacturer	Indication	Date Approved
Anidulafungin	Eraxis	Pfizer	Candidemia, other forms of Candida infections, esophageal candidiasis	2/17/2006
Avobenzone, ecamsule and octocrylene cream	Anthelios SX	L'Oréal	Triple combination, moisturizing sunscreen with UVA and UVB protection	7/21/2006
Bismuth subcitrate potassium/metronidazole/ tetracycline	Pylera	Axcan	Eradication of <i>H. pylori</i>	9/28/2006
Ciclesonide	Omnaris	Altana	Allergic rhinitis	10/20/2006
Darunavir	Prezista	Johnson & Johnson	HIV infection	6/23/2006
Dasatinib	Sprycel	Bristol-Myers Squibb	Chronic myelogenous leukemia	6/28/2006
Decitabine injection	Dacogen	MGI/SuperGen	Myelodysplastic syndrome	5/2/2006
Kunecatechins	Veregen	MediGene	Genital and perianal warts	10/31/2006
Lubiprostone	Amitiza	Sucampo (Takeda co-promote)	Chronic idiopathic constipation	1/31/2006
Paliperidone	Invega	Johnson & Johnson	Schizophrenia	12/19/2006
Posaconazole	Noxafil	Schering-Plough	Disseminated candidiasis, <i>Aspergillus</i> species	9/15/2006
Ranolazine	Ranexa	CV Therapeutics	Chronic angina	1/27/2006
Rasagiline	Azilect	Teva	Parkinson's disease	5/16/2006
Sitagliptin	Januvia	Merck	Type 2 diabetes mellitus	10/16/2006
Sunitinib	Sutent	Pfizer	Gastrointestinal stromal tumors, advanced renal cell carcinoma	1/26/2006
Telbivudine	Tyzeka	Novartis/Idenix	Chronic hepatitis B	10/26/2006
Varenicline	Chantix	Pfizer	Smoking cessation	5/10/2006
Vorinostat	Zolinza	Merck	Advanced cutaneous T-cell lymphoma	10/6/2006

Adapted from the FDA (www.fda.gov/cder/rdmt/InternetNDA06.htm) and FDC's Pharmaceutical Approvals Monthly, January 2007 issue