



The University of Florida College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education
**ACPE # 012-999-06
016-H01**

This lesson is no longer valid for CE credit after 2/29/08.

To obtain immediate CE credit, take the test on-line at **www.drugtopics.com**. Just click on the "Continuing Education" box on the *Drug Topics* home page, which will take you to the CE site. Log in, find and click on this lesson, and follow the three simple steps. Test results will be displayed immediately and you can print the certificate showing your earned CE credits.



New drug update 2005 – Part 2

Paul L. Doering, M.S., Distinguished Service Professor of Pharmacy Practice, Codirector, Drug Information and Pharmacy Resource Center, College of Pharmacy, University of Florida, Gainesville, Fla.

Lisa A. Boothby, Pharm.D., BCPS, Affiliate Clinical Assistant Professor, Auburn University, Harrison School of Pharmacy, Drug Information Coordinator, Columbus Regional Drug Information Center, Columbus, Ga.

This continuing education article, Part 2, will review the remaining new molecular entities (NMEs) approved by the Food & Drug Administration in 2005 that were not covered in Part 1 (*Drug Topics*, Feb. 6). Some of the NMEs the FDA deemed significant improvements over current marketed products include two novel chemotherapy agents; an antibiotic for severe, resistant infections; an agent to treat rheumatoid arthritis; and two new biologic agents. (See Part 1 for a table of the NMEs for 2005.)

GOAL

To review the new molecular entities approved by the Food & Drug Administration in 2005

CREDIT

This lesson provides two hours of CE credit and requires a passing grade of 70%.*

OBJECTIVES

Upon completion of this article, the pharmacist should be able to:

- ✓ List the name, mechanism of action, pharmacological properties, potential drug interactions, route of administration, dosing schedule, and dosage forms for the new drugs reviewed
- ✓ Outline potential adverse drug reactions, monitoring parameters, and salient points for patient discussion during counseling sessions

*To receive credit you must score 70% or higher on the quiz and complete the evaluation. Upon successful completion, the University of Florida College of Pharmacy will mail Statements of Credit for written quizzes within 10 working days. Participants completing the program on-line may print a Statement of Credit after successfully completing the program.

For questions concerning PRINT CEs, call (352) 273-6275.
For questions concerning ON-LINE CEs, call (866) 261-3558.

CONTINUING EDUCATION

ABATACEPT (Bristol-Myers Squibb) Orencia FDA rating: 1-P (P = priority review)

Abatacept, a biologic agent, is the first in a new class of selective co-stimulation modulators. It inhibits the action of T-cells in patients with severe rheumatoid arthritis (RA).

Indications: Abatacept is indicated for patients with RA who have had inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs) such as methotrexate or tumor necrosis factor (TNF) antagonists.

Pharmacology: A selective co-stimulator modulator, abatacept binds to CD80 and CD86 to block the interaction with CD28, required for full T-lymphocyte (T-cell) activation. Activated T cells have been found in the synovium of patients with RA and are implicated in the pathogenesis of the disease.

Precautions: The use of abatacept is associated with an increased risk of developing infections, especially upper respiratory infections. If a patient develops a serious infection, sepsis, signs of hematologic disease (i.e., agranulocytosis or persistent fever, bleeding, bruising, or pallor) or if significant hematologic abnormalities are confirmed during abatacept therapy, the drug should be discontinued.

As malignancy is a possible risk of immunosuppressive therapy, practitioners should exercise caution in prescribing abatacept to patients with a history of malignancies. Abatacept should be used during pregnancy only if clearly needed. Breast-feeding women should not take abatacept.

Drug interactions: Concomitant methotrexate, non-steroidal anti-inflammatory drugs, corticosteroids, and TNF-blocking agents did not affect abatacept clearance in clinical trials. Concomitant use of abatacept and anakinra is not recommended since safety and efficacy of this combination have yet to be adequately studied. The manufacturer advises not administering abatacept with adalimumab, etanercept, or infliximab, since patients receiving concomitant abatacept and TNF-antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared with patients treated with only TNF antagonists (43% and 0.8%, respectively).

The manufacturer recommends monitoring patients for signs of infection during the transition from TNF-antagonist therapy to abatacept therapy. Further, live vaccines should not be given concurrently with abatacept or within three months of its discontinuation, since abatacept may blunt the effectiveness of immunizations.

Adverse effects: The most commonly observed adverse events occurring in at least 10% of patients treated with abatacept included headache, upper respiratory tract infection, nasopharyngitis, and nausea. Infusion reactions occurred in 9% of patients, and the incidence of dizziness, headache, and hypertension ranged from 1% to 2%.

Dosage: Abatacept is administered as a 30-min. infusion at a fixed dose based on weight range (approx. 10-mg/kg) at day 0, two weeks, and every four weeks thereafter.

Patient counseling: Tell patients that abatacept is for infusion into a vein. It is administered in a hospital or clinic setting by a healthcare professional.

CONIVAPTAN HYDROCHLORIDE (Astellas) Vaprisol FDA rating: 1-PO (O = orphan drug)

Conivaptan is a novel infusion therapy for patients with euvolemic hyponatremia.

Indications: Conivaptan hydrochloride injection is a non-peptide, dual antagonist of arginine vasopressin (AVP) V1a and V2 receptors. It is indicated for the treatment of euvolemic hyponatremia (e.g., the syndrome of inappropriate secretion of antidiuretic hormone, or, in the setting of hypothyroidism, adrenal insufficiency, pulmonary disorders, etc.) in hospitalized patients.

Pharmacology/pharmacokinetics: Conivaptan hydrochloride is a dual AVP antagonist with nanomolar affinity for human V1a and V2 receptors in vitro. The arginine vasopressin effect is mediated through V2 receptors, which are functionally coupled to aquaporin channels in the apical membrane of the collecting ducts of the kidney. These receptors help maintain plasma osmolality within normal range.

Conivaptan is extensively bound to human plasma proteins, being 99% bound over the concentration range of approximately 10 to 1000 ng/ml. CYP3A4 was identified as the sole cytochrome P450 isozyme responsible for the metabolism of conivaptan. Four metabolites have been identified. After intravenous (10 mg) or oral (20 mg) administration of conivaptan hydrochloride in a mass balance study, approximately 83% of the dose was excreted in feces and 12% in urine over several days of collection. Following oral conivaptan administration, the AUC was up to 80% higher in patients with renal impairment (CrCl <60 ml/min.) compared with those with normal renal function.

Precautions: Conivaptan is contraindicated in patients with hypovolemic hyponatremia. Use conivaptan with caution in patients with hepatic disease, renal impairment, or in women who are pregnant or breast-feeding.

Drug interactions: Conivaptan is a substrate of CYP3A4. Coadministration of conivaptan with CYP3A4 inhibitors could lead to an increase in conivaptan concentrations. Concomitant use of conivaptan with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir is contraindicated.

Conivaptan is also a potent inhibitor of CYP3A4. In clinical trials of oral conivaptan hydrochloride, two cases of rhabdomyolysis occurred in patients also receiving a

CYP3A4-metabolized HMG-CoA reductase inhibitor.

Adverse effects: Even with proper dilution and infusion rates, conivaptan may cause significant injection-site reactions.

Dosage and availability: As a loading dose, withdraw 4 ml (20 mg) of conivaptan. Add to an infusion bag containing 100 ml of 5% Dextrose Injection, USP. Contents of the IV bag should be administered over 30 minutes. As a continuous infusion, prepare an infusion containing 20 mg conivaptan hydrochloride by withdrawing 4 ml (20 mg) from a single ampule of conivaptan and diluting into an IV bag containing 250 ml of 5% Dextrose Injection, USP. Contents of the IV bag should be administered over 24 hours.

Patient counseling: A healthcare professional will be administering this medication. Ask patients for a complete medication history, as conivaptan has several clinically significant drug interactions.

GALSULFASE (Biomarin)
Naglazyme FDA rating: 1-P0

Galsulfase, a biologic agent, is administered as an IV infusion once weekly to relieve some symptoms of mucopolysaccharidosis, such as improved physical stamina.

Indications: Galsulfase is the first FDA-approved enzyme replacement therapy indicated for the treatment of patients with mucopolysaccharidosis (MPS) type VI.

Pharmacology: MPS disorders are caused by a lack of lysosomal enzymes necessary for the breakdown of glycosaminoglycans (GAG). Accumulation of GAG leads to widespread cellular, tissue, and organ dysfunction in patients with MPS. Galsulfase provides an exogenous enzyme that is taken up into lysosomes and increases the breakdown of GAG.

Precautions: Galsulfase should be used cautiously in patients with hamster protein hypersensitivity (Chinese hamster ovary, or CHO, cell hypersensitivity), galsulfase hypersensitivity, or hypersensitivity to other components of the product, due to increased risk of severe allergic reactions.

Drug interactions: There are none known. No drug interaction studies were performed.

Adverse effects: Infusion-related reactions occurred in approximately 55% of patients receiving galsulfase in clinical trials, despite pretreatment with antihistamines. Severe infusion-related symptoms included angioedema (facial edema, 11%), hypotension, dyspnea (21%), bronchospasm, respiratory distress, apnea, and urticaria.

Dosage and availability: For the treatment of mucopolysaccharidosis VI in adults, adolescents, and children \geq five years old, administer 1 mg/kg IV infused over no less than four hours once per week. Administer at a rate of 6 ml/hr

for the first hour. If an infusion-related reaction occurs, the infusion time can be extended to up to 20 hours. Pretreatment with an antihistamine with or without antipyretics is recommended prior to the start of infusion.

Patient counseling: Ask patients if they suffer from sleep apnea, and if they have a fever or an infection. Patients should inform their healthcare provider if they have had an unusual reaction to human or hamster proteins in the past. Galsulfase is for injection into a vein. Tell patients that it is given as an infusion by a healthcare professional in a hospital or clinic setting.

HYALURONIDASE, RECOMBINANT (Halozyme Therapeutics)
Hylenex FDA rating: 1-P

Recombinant human hyaluronidase (Hylenex) is now available in addition to Amphadase (bovine), Vitrase (ovine), and Hydase (bovine) hyaluronidase.

According to the company, results from a clinical trial conducted to support the Hylenex NDA demonstrated no allergic reactions to Hylenex and significantly reduced injection site discomfort. Otherwise, the profile of this drug is virtually identical to the other forms of hyaluronidase.

The FDA considers all hyaluronidase products as new molecular entities because there are variations among their chemical compositions.

The reader is referred to Part 1 of the New Drug Update (Drug Topics, Feb. 6, 2006) for details on this agent.

LENALIDOMIDE (Celgene Corp.)
Revlimid FDA rating: 1-P

Lenalidomide is an oral anticancer medication that is chemically similar to thalidomide.

Indications: Lenalidomide is approved to treat a subgroup of patients with myelodysplastic syndrome. This product is chemically similar—but not identical—to thalidomide. Lenalidomide is indicated for patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndrome associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. It is also currently being evaluated in at least 17 clinical trials for other indications as of January 2006.

Pharmacology/pharmacokinetics: Although the mechanism of action of lenalidomide has yet to be fully characterized, it is known to possess immunomodulatory and antiangiogenic properties. Lenalidomide is rapidly absorbed following oral administration. In vitro, lenalidomide exhibits approximately 30% plasma protein binding. Approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion with an elimination half-life of approximately three hours.

Precautions: The package insert contains several important black box warnings, including information about the following: (1) potential for human birth defects, (2) hematologic toxicity (neutropenia and thrombocytopenia), and (3) deep venous thrombosis and pulmonary embolism. Since lenalidomide is an analog of thalidomide—and thalidomide is a known human teratogen that causes severe life-threatening human birth defects—if lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Due to the teratogenicity potential, lenalidomide is available only under a special restricted distribution program called “RevAssist.” Under this program, only prescribers and pharmacists registered with the program are able to prescribe and dispense the product.

Drug interactions: Lenalidomide is neither metabolized by nor does it inhibit or induce the cytochrome P450 pathway, suggesting that the drug is not likely to cause or be subject to P450-based metabolic drug interactions.

Adverse effects: The most frequently reported adverse events associated with lenalidomide are thrombocytopenia (61.5%) and neutropenia (58.8%). The next most frequent include diarrhea, pruritus, rash, fatigue, constipation, nausea, nasopharyngitis, arthralgia, pyrexia, back pain, peripheral edema, cough, dizziness, headache, muscle cramp, dyspnea, and pharyngitis.

Dosage and availability: The recommended initial dose for lenalidomide is 10 mg daily. Dose adjustments should be based upon clinical and laboratory findings. The FDA recommends weekly monitoring of complete blood counts for the first eight weeks of therapy and at least monthly thereafter; some patients may require supplemental blood products and/or growth factors.

Lenalidomide is available as 5-mg or 10-mg oral capsules.

Patient counseling: A medication guide must be given to patients with each prescription, and the pharmacist should take this opportunity to explain the potential risks to patients when lenalidomide is dispensed.

The use of two effective methods of contraception concurrently is recommended to avoid pregnancy. All females of childbearing potential must pass a test at the start of treatment and each subsequent month of treatment thereafter to ensure they understand pregnancy prevention and that their risk of fetal exposure is low. The test is conducted over the telephone. In addition, before starting lenalidomide, females of childbearing potential must sign (along with the physician) an agreement to show they understand the need to avoid pregnancy while taking lenalidomide. Two negative pregnancy tests must be documented by their physician prior to the start of lenalidomide therapy.

The first test should be performed within 10-14 days and the second test within 24 hours prior to the prescribing of lenalidomide.

MECASERMIN RINFABATE (Inmed Inc.) iPlex for injection FDA rating: 1-PO

Mecasermin, an orphan drug, is an injectable agent for the treatment of growth failure in children.

Indications: Mecasermin is indicated for treating growth failure in children with severe primary IGF-1 deficiency (primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

Pharmacology: Mecasermin, a binary protein complex of human insulin-like growth factor-1 (rh-IGF-1) and human insulin-like growth factor-binding protein-3 (rh-IGFBP-3), is a recombinant product identical in chemical structure and activity to endogenous human insulin-like growth factor-1 (IGF-1) bound with its major binding protein human insulin-like growth factor-binding protein-3 (IGFBP-3). Under normal conditions, IGF-1 mediates growth hormone (GH) activity both locally, as a growth factor in the tissues where it is produced, and systemically, as a hormone in target tissues throughout the body.

Precautions: Therapy with mecasermin should be directed by physicians experienced in the diagnosis and management of patients with growth disorders.

As with any exogenous protein administration, local or systemic allergic reactions may occur. Parents and patients should be informed that such reactions are possible and that if an allergic reaction occurs, treatment should be interrupted and prompt medical attention should be sought.

Drug interactions: Use caution in coadministering mecasermin with antidiabetic agents, since a hypoglycemic effect may be exacerbated in some patients.

Adverse effects: Overt changes in facial appearance, facial edema, increases in hair growth or texture, and soft tissue thickening of the face and an increase in the prominence of the eyebrow ridge (glabella), eyebrows, nasal tip, and lips may occur during mecasermin therapy. Injection-site reactions were commonly reported, including erythema, lipohypertrophy, and hair growth at the site of injection.

Hypoglycemia was reported in 11 of 36 patients (31%) in clinical trials and was generally rated as mild and asymptomatic. In clinical trials, headache was reported in eight of 36 patients (22%). Tonsillar and/or adenoid hypertrophy, was noted in seven of 36 patients (19%) in clinical trials.

Increased size of the liver, kidney, and spleen (splenomegaly) has been noted in several patients via abdominal ultrasound. In these patients, renal function was normal.

Five percent or more of patients reported bone pain, pain in extremities, arthralgia, and muscular atrophy during treatment with mecaseermin. Iron deficiency anemia and hematuria were common treatment-related adverse events occurring in two or more (greater than 5%) patients in clinical trials. Elevated hepatic enzymes, including mild elevations in serum AST and LDH, were found in a significant proportion of patients before and during treatment.

Dosage and availability: For children three years of age or older: initially, administer 0.5 mg/kg once daily by subcutaneous injection at approximately the same time every day. Titrate the dose based on IGF-1 concentrations, obtained eight to 18 hours post dose, to within the therapeutic range of 1 to 2 mg/kg daily, not to exceed 2 mg/kg daily.

Mecasermin should be administered at approximately the same time every day. Because it has insulin-like hypoglycemic effects, patients should avoid missing meals and should have a balanced diet. Mecasermin should not be given on days when the patient cannot or will not eat.

This medicine will be shipped frozen to the patient or to the physician's office. It should be kept frozen at all times until the patient is ready to use it. Mecasermin should be stored in the freezer at -4°F or colder for a maximum of two months. Once the medicine thaws, it must be used within one hour. If the vial of mecaseermin has been out of the freezer for more than two hours, it should be discarded.

Patient counseling: Inform patients this medicine is given as an injection under the skin. It is never to be injected into a vein or muscle. Tell patients or caregivers how to inject mecaseermin and to use the medicine at about the same time each day.

PRAMLINTIDE ACETATE (Amylin)

Symlin

FDA rating: 1-S (S = standard review)

Used in combination with insulin, pramlintide is associated with modest weight reductions during therapy.

Indications: Pramlintide acetate is indicated for patients with Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy who have failed to achieve desired glucose control despite optimal insulin therapy, and as an adjunct treatment in Type 2 diabetes patients who use mealtime insulin therapy who have failed to achieve desired glucose control despite optimal insulin therapy with or without a concurrent sulfonylurea agent and/or metformin.

Pharmacology: Pramlintide is a synthetic analog of amylin synthesized from a chemical modification of amylin with proline substituted for three amino acid residues at positions 25, 28, and 29. Amylin itself cannot be injected, as it is too viscous, is unstable in solution, and tends to aggregate. Pramlintide acts to moderate glucose

absorption, slowing and managing meal-derived glucose inflow, controlling pancreatic glucagon secretion, which in turn regulates hepatic glucose production. It also suppresses after-meal release of glucose from the liver. Both of these activities serve to "smooth the peaks and valleys" of blood sugar fluctuation and improve overall glycemic control.

Precautions: Pramlintide should not be used in patients who have poor compliance with their current insulin regimen, poor compliance with prescribed self-monitoring of blood glucose (SMBG), or poorly controlled diabetes mellitus as evidenced by a glycosylated hemoglobin $>9\%$. In addition, pramlintide should be discontinued if recurrent unexplained hypoglycemia that requires medical assistance, persistent nausea, or noncompliance with SMBG, insulin dose adjustments, or recommended follow-up occurs during therapy. Because pramlintide slows the rate of gastric emptying, patients should not use pramlintide if they have been diagnosed with gastroparesis or if they require the use of drugs that stimulate gastrointestinal motility. When introducing pramlintide therapy, appropriate precautions need to be taken to reduce the risk of severe insulin-induced hypoglycemia. The precautions include an increase in the frequency of blood glucose monitoring and a reduction in the mealtime insulin dose.

Drug interactions: Monitor blood glucose for needed dosage adjustments in diabetic patients whenever a change in either nicotine intake or tobacco smoking status occurs, since nicotine use can affect insulin sensitivity. When acetaminophen was administered one to two hours before pramlintide administration, the T_{\max} was not significantly altered; the T_{\max} was increased when acetaminophen was administered within two hours of pramlintide injection.

According to the maker, insulin and pramlintide should not be combined in the same syringe or administered in the same injection site, as the pharmacokinetic parameters of pramlintide are altered by regular, isophane (NPH), and premixed 70/30 insulin formulations. Disopyramide may enhance the hypoglycemic effects of pramlintide.

Adverse effects: Hypoglycemia is the most frequently reported adverse reaction during clinical trials of pramlintide. This drug by itself does not cause hypoglycemia; however, when pramlintide is used in combination with insulin, the risk of insulin-induced hypoglycemia is increased. While the risk of severe hypoglycemia appears to be higher in patients with Type 1 diabetes, patients with Type 2 diabetes can also experience severe hypoglycemia. Severe hypoglycemia with pramlintide therapy is most common during pramlintide initiation (i.e., the first four weeks of therapy) and in the first three hours following injection.

CONTINUING EDUCATION

Other adverse events reported with a frequency of $\geq 5\%$ in pramlintide-treated patients and greater than that of placebo include arthralgia, coughing, dizziness, fatigue, headache, inflicted injury, and pharyngitis.

Dosage and availability: In patients with Type 1 diabetes, pramlintide should be initiated at a dose of 15 mcg and titrated at 15-mcg increments to a maintenance dose of 30 mcg or 60 mcg, as tolerated. For patients with Type 2 diabetes using insulin, pramlintide should be initiated at a dose of 60 mcg and increased to a dose of 120 mcg as tolerated. Pramlintide is supplied as a sterile injection in 5-ml vials, containing 0.6 mg/ml pramlintide (as acetate). Pramlintide should be administered subcutaneously immediately prior to each major meal (greater than or equal to 250 kcal or containing greater than or equal to 30 gm of carbohydrate). Before use, pramlintide vials should be refrigerated and protected from light. According to the manufacturer, if a vial has been frozen or overheated, throw it away.

Patient counseling: Patients should read the medication guide that comes with pramlintide before they start using the drug and at each refill. Inform patients that pramlintide is given at mealtimes, and that the use of pramlintide does not replace the need for daily insulin injections but may lower the amount of insulin the patient needs. Patients and caregivers should know that even when pramlintide is carefully added to mealtime insulin therapy, blood sugar may drop too low, especially in patients with Type 1 diabetes. If this low blood sugar (severe hypoglycemia) occurs, it is usually observed within three hours after a pramlintide injection. Remind patients and caregivers that severe low blood sugar makes it hard to think clearly. Caution should be used in driving a car, using heavy machinery, or performing other potentially risky activities. Patients should be told never to mix pramlintide and insulin. Also inform patients that alcohol use may increase the risk of hypoglycemia.

RAMELTEON (Takeda Global) **Rozerem** FDA rating: 1-S

Ramelteon is the first in a new class of agents termed melatonin receptor agonists, and it is the first approved hypnotic not classified as a controlled substance.

Indications: Ramelteon is a highly selective, potent MT1 and MT2 melatonin receptor agonist approved for the treatment of insomnia due to prolonged sleep onset.

Pharmacology/pharmacokinetics: Ramelteon selectively targets the melatonin receptors MT1 and MT2, which are believed to be involved in the regulation of the circadian rhythm. Unlike the benzodiazepines, ramelteon has not been shown to decrease rapid eye movement (REM) sleep. Ramelteon is administered orally and exhibits linear pharmacokinetics. It is absorbed rapidly, with median peak

concentrations occurring at approximately 0.75 hours after fasted oral administration. A high-fat meal can alter the oral absorption of ramelteon.

Precautions: Ramelteon should not be taken with a high-fat meal, due to altered absorption. It should not be used in populations with severe sleep apnea or severe chronic obstructive pulmonary disease (COPD). Patients should use caution if they consume alcohol while taking ramelteon.

Drug interactions: Due to ramelteon's being metabolized by the cytochrome P450 enzyme system (primarily CYP1A2), there is the potential for clinically significant drug interactions. Thus, ramelteon should not be used in combination with fluvoxamine, a strong CYP1A2 inhibitor. Theoretically, ramelteon should be administered with caution to patients taking other CYP1A2 inhibitors such as ciprofloxacin, enoxacin, mexiletine, norfloxacin, tacrine, and zileuton, among others. Efficacy may be reduced when ramelteon is used in combination with strong CYP1A2 enzyme inducers, such as rifampin or CYP1A2 inhibitor, such as ethinyl estradiol. Theoretically, similar interactions may occur with barbiturates and carbamazepine. Tobacco use may also result in induction of the CYP1A2 isozyme and may theoretically result in reduced serum concentrations of ramelteon. Ramelteon should be administered with caution in subjects taking CYP2C9 inhibitors, such as fluconazole, imatinib, miconazole, voriconazole, and zafirlukast, as well as CYP3A4 inhibitors, such as ketoconazole.

Adverse effects: Ramelteon appears to be well tolerated at 8 mg orally, once daily. In safety clinical trials ($n=2620$), the most frequent adverse events observed were similar to those in the placebo group. Ramelteon use may be associated with adrenocortical insufficiency.

Dosage and availability: The recommended dose for adults and the elderly is ramelteon 8 mg taken at bedtime. The safe and effective dose has not been established for adolescents or children. Patients with severe hepatic impairment should not use ramelteon. Also, ramelteon should be used with caution in patients with moderate liver disease, although specific dosage-adjustment recommendations are not available. Ramelteon is supplied as an 8-mg tablet.

Patient counseling: Patients should be advised to take ramelteon within 30 min. of retiring for the night. They should avoid hazardous activities (such as operating a motor vehicle) after taking ramelteon. Ramelteon should not be taken with or immediately after a high-fat meal.

SORAFENIB TOSYLATE (Bayer Pharmaceuticals) **Nexavar** FDA rating: 1-PO

Sorafenib tosylate is a new anticancer drug used to treat adults with advanced renal cell carcinoma, the most com-

mon type of kidney cancer.

Indications: Sorafenib is FDA-approved for the treatment of advanced renal cell carcinoma, the most common type of kidney cancer. It is currently being investigated in approximately 50 clinical trials for the treatment of numerous neoplastic diseases.

Pharmacology: Sorafenib is a multikinase inhibitor that targets serine/threonine and receptor tyrosine kinases to decrease tumor growth and angiogenesis. Preclinical models demonstrated the drug's activity against RAF kinase, VEGFR-2, VEGFR-3, PDGFR-B, KIT, and FLT-3.

Precautions: Weekly monitoring of blood pressure is recommended during the first six weeks of treatment. Because sorafenib may also be linked to an increased risk for bleeding, patients receiving concomitant warfarin therapy should be monitored regularly. Sorafenib should be used cautiously in patients who have had previous myelosuppressive therapy such as chemotherapy or radiation therapy. Bone marrow suppression, including neutropenia and thrombocytopenia, has been reported with sorafenib. Use with caution in patients with active bleeding, including GI bleeding. Patients with active infection, including fungal infection or viral infection, should be treated prior to receiving sorafenib. Patients with a history of varicella zoster, other herpes infection (e.g., herpes simplex), or other viral infection are at risk for reactivation of the infection when treated with chemotherapy.

Patients treated with sorafenib should not receive intramuscular injections, as bleeding, bruising, or hematomas, due to sorafenib-induced thrombocytopenia, may result. Sorafenib is classified as FDA pregnancy risk category D.

Sorafenib should be assumed to cause human fetal harm, based on animal data and also on the proposed mechanism of multikinase inhibition. Females of childbearing potential should be advised to avoid becoming pregnant while receiving sorafenib, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Breast-feeding is not recommended during sorafenib treatment. The safety and efficacy of sorafenib have not been determined in pediatrics. Use with caution in patients with hepatic disease, jaundice, or renal disease (CrCl <30 ml/min).

Drug interactions: Coadministration of sorafenib with doxorubicin resulted in a 21% increase in the doxorubicin AUC. Although the clinical significance of these findings is unknown, close clinical monitoring of patients receiving sorafenib and doxorubicin is recommended. When sorafenib was administered with irinotecan, there was a 26%-42% increase in the irinotecan AUC. Although the clinical significance of these findings is unknown, close clinical monitoring of patients receiving sorafenib with

irinotecan is recommended. Sorafenib may be safely coadministered with ketoconazole. Theoretically, any drug that induces CYP3A4 may increase the metabolism of sorafenib and decrease sorafenib concentrations and clinical effects. Sorafenib is a competitive inhibitor of CYP2C9 and may increase concentrations of other drugs metabolized by this enzyme. Caution is recommended when administering sorafenib with other CYP2C9 substrates having a narrow therapeutic range, such as celecoxib, diclofenac, dronabinol, THC, phenytoin or fosphenytoin (also CYP3A4), piroxicam, sertraline (also CYP3A4), tolbutamide, topiramate, and S-warfarin, or where large increases in concentrations may be associated with severe adverse reactions.

Adverse effects: Some common temporary side effects reported with sorafenib include rash, diarrhea, increases in blood pressure, and redness, pain swelling, or blisters on the palms of the hands or soles of the feet. The most commonly reported treatment-related adverse events of any severity included diarrhea, rash/desquamation, fatigue, hand-foot skin reaction, alopecia, nausea, pruritus, hypertension, vomiting, and anorexia. Grades 3 and 4 adverse events were reported in 31% and 7% of patients receiving sorafenib, compared with 22% and 6%, respectively, of those administered placebo.

Dosage and availability: The recommended dose of sorafenib for the treatment of renal cell carcinoma is 400 mg orally twice daily without food, at least one hour before or two hours after eating. The manufacturer recommends that treatment continue for as long as it is effective or until unacceptable toxicity occurs. If toxicity occurs that necessitates dose reduction, 400 mg once a day or 400 mg every other day may be used. To order sorafenib, hospitals or clinics are instructed to contact their local sales representative from Bayer Pharmaceuticals.

Patient counseling: A patient information sheet is included with the package insert and should be given to the patient with each prescription for sorafenib. Explain to both male and female patients the importance of appropriate birth control methods to prevent pregnancy. Tell patients to wait at least two weeks after sorafenib discontinuation before trying to become pregnant. Tell patients to take sorafenib whole with water on an empty stomach. If the patient forgets to take a dose, that dose should be skipped; do not double the next dose. If a rash develops on the hands and feet, have the patient contact his physician immediately.

TIGECYCLINE (Wyeth Pharmaceuticals)

Tygacil

FDA rating: 1-P

Tigecycline is an intravenous glycylicycline antibiotic derived from minocycline. It is used for certain severe infec-

tions that may be resistant to older antibiotics.

Indications: Tigecycline is indicated for the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections caused by susceptible strains of designated microorganisms in patients 18 years of age and older.

Pharmacology/pharmacokinetics: The mechanism of action of tigecycline is similar to the tetracyclines except that tigecycline binds five times more strongly to the ribosome compared with tetracycline or minocycline. Tigecycline differs from minocycline by a glycyamido moiety attached to the nine-position of minocycline. This substitution is not present in any naturally occurring or semisynthetic tetracycline and imparts certain microbiologic properties to tigecycline. Indeed, tigecycline shows activity against tetracycline-resistant organisms exhibiting genes for efflux and ribosomal resistance mechanisms, the two major tetracycline resistance mechanisms.

Other resistance mechanisms, such as beta-lactamases (including extended-spectrum beta-lactamases), target-site modifications, macrolide efflux pumps, or enzyme target changes (e.g., gyrase/topoisomerase) do not affect the activity of tigecycline. The spectrum of activity of tigecycline includes gram-positive, gram-negative, and anaerobic microorganisms. Tigecycline exhibits broad-spectrum coverage, including coverage for gram-positive, gram-negative, and anaerobic microorganisms. Some of the aerobic gram-negative organisms for which tigecycline has been shown to be active in vitro and in clinical infections include *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, and *K. pneumoniae*. Other aerobic gram-negative organisms for which tigecycline has shown in vitro activity include *Acinetobacter baumannii*, *Aeromonas hydrophila*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Pasteurella multocida*, *Serratia marcescens*, and *Stenotrophomonas maltophilia*. *Pseudomonas aeruginosa* is resistant to tigecycline.

Approximately 22% of an administered dose is excreted unchanged in the urine. The mean elimination half-life ranges from about 27 hours following a single 100-mg dose to 42 hours after multiple doses.

Precautions: Tigecycline may cause fetal harm when administered to a pregnant woman. The use of tigecycline during tooth development (last half of pregnancy, infancy, and childhood to the age of eight years) may cause permanent discoloration of the teeth (yellow gray-brown). Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening.

Drug interactions: Based on data from in vitro studies, tigecycline does not inhibit metabolism mediated by any cytochrome P450 enzymes. Tigecycline did not significantly alter the effects of warfarin on the International Normalized

Ratio (INR) in this single-dose study. Warfarin did not affect the pharmacokinetic profile of tigecycline.

Adverse effects: In clinical trials with tigecycline, the most common treatment-emergent adverse events were nausea and vomiting, which generally occurred during the first one to two days of therapy. The majority of cases of nausea and vomiting associated with tigecycline and comparators were either mild or moderate in severity. In patients treated for complicated skin and skin structure infections, nausea incidence was 35% for tigecycline and 8.9% for vancomycin/aztreonam; vomiting incidence was 20% for tigecycline and 4.2% for vancomycin/aztreonam. In patients treated for complicated intra-abdominal infections, nausea incidence was 25.3% for tigecycline and 20.5% for imipenem/cilastatin; vomiting incidence was 19.5% for tigecycline and 15.3% for imipenem/cilastatin.

Dosage and availability: Tigecycline for injection is supplied in a single-dose 5-ml glass vial containing 50 mg lyophilized powder for reconstitution. The recommended dosage regimen for tigecycline is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous (IV) infusions of tigecycline should be administered over approximately 30 to 60 minutes every 12 hours. The recommended duration of treatment with tigecycline for complicated skin and skin structure infections or for complicated intra-abdominal infections is five to 14 days. The duration of therapy should be guided by the severity and site of the infection and the patient's clinical and bacteriological progress. No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response. No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Patient counseling: Tell patients that tigecycline injection solution is for infusion into a vein. It is usually given first in a hospital or clinic and is used only for severe infections. Patients should inform their physician or pharmacist if they have intestinal disease, liver disease, are pregnant or breast-feeding. Once tigecycline therapy is started, have patients contact the nurse if they experience difficulty breathing, irregular heartbeat, dizziness, rash, swelling of the hands or feet, or yellowing of the skin.

For further information on the new molecular and biologic entities the FDA approved in 2005, see the FDA Web site at <http://www.fda.gov/cder/rdmt/ndaaps05cy.htm>.

References available upon request

TEST QUESTIONS

Write your answers on the answer form appearing on page 52 (photocopies of the answer form are acceptable) or on a separate sheet of paper. Mark the most appropriate answer.

- Abatacept is the first-in-class selective co-stimulation modulator that inhibits the action of T cells in patients with:
 - Osteoarthritis
 - Multiple sclerosis
 - Amyotrophic lateral sclerosis
 - Severe rheumatoid arthritis
- Patients taking abatacept can safely receive which one of the following drugs?
 - Adalimumab
 - Etanercept
 - Infliximab
 - None of the above can be safely used with abatacept
- The typical community pharmacist is not apt to dispense abatacept because it should be administered in a hospital or clinic setting by a healthcare professional.
 - True
 - False
- Conivaptan is a new treatment for patients with euvolemic hyponatremia that works by:
 - Inhibiting prostaglandin-mediate tubular reabsorption
 - Antagonizing the actions of arginine vasopressin (AVP) V1a and V2 receptors
 - Suppressing release of oxytocin from the posterior pituitary
 - Antagonizing antidiuretic hormone (ADH)
- Conivaptan is contraindicated in patients with:
 - Hypochloremic hyperkalemia
 - Hypochloremic hypokalemia
 - Hypovolemic hyponatremia
 - Hypovolemic hypermagnesemia
- Conivaptan is a substrate of which enzyme (and hence coadministration of this drug with inhibitors of this enzyme could lead to an increase in conivaptan concentrations)?
 - CYP2D6
 - CYP3A4
 - CYP2D9
 - CYP2D7
- Galsulfase is the first FDA-approved enzyme replacement therapy that is indicated for the treatment of patients with:
 - Mucopolysaccharidosis type VI
 - Alzheimer's disease (subtype II)
 - Polymicrobial mucormycosis
 - Type 2 sarcoidosis
- Galsulfase is administered:
 - As an Intravenous bolus
 - As an intravenous infusion over at least four hours
 - Every eight hours orally
 - As an intradermal injection
- Lenalidomide is an oral anticancer medication that is chemically similar to:
 - Sulfanilamide
 - Tolbutamide
 - Cyclophosphamide
 - Thalidomide
- Mecasermin is an orphan drug that is an injectable agent for the treatment of:
 - Pituitary tumors of the Rosenfeld type
 - Growth failure in children
 - Type 2 diabetes mellitus
 - Type 2 histiocytosis
- Patients using mecasermin should avoid missing meals and should have a balanced diet, because the agent has:
 - Insulin-like hypoglycemic effects
 - A tendency to produce hyperglycemia
 - Better absorption when given with meals
 - Better tolerance when given without meals
- Pramlintide, like amylin, a hormone produced in the beta cells of the pancreas, appears to have a moderating effect on:
 - Glucose absorption from the gut into the blood
 - Increasing glycogenolysis in the liver
 - Decreasing gluconeogenesis
 - All of the above
- What is the most frequently reported adverse reaction during clinical trials of pramlintide?
 - Hyperglycemia
 - Heptatotoxicity
 - Renal toxicity
 - Hypoglycemia
- Patients should be instructed that pramlintide should be given:
 - At mealtimes
 - At bedtime
 - Upon arising and taken only with water
 - The timing of administration is not important
- Ramelteon is the first in a new class of agents termed:
 - Melatonin receptor agonists
 - CB-1 antagonists
 - Raphae nuclei antagonists
 - Nucleus accumbans agonists
- Ramelteon should not be used in combination with which strong CYP1A2 inhibitor?
 - flurazepam
 - fluvoxamine
 - fludarabine
 - ludrocortisone
- Ramelteon is approved for the treatment of insomnia due to:
 - Decreased duration of sleep
 - Early morning awakenings
 - Prolonged sleep onset
 - All of the above
- The mechanism of action of tigecycline is similar to the tetracyclines in that it binds strongly to:
 - Cell-wall components of bacteria
 - Bacterial ribosomes
 - DNA gyrase
 - Bacterial protease

TEST QUESTIONS

- 19.** Tigecycline significantly alters the effects of warfarin on the INR as evidenced by clinical trial results.
 a. True
 b. False
- 20.** Based on data from in vitro studies, tigecycline has been shown to inhibit metabolism mediated by which of the following cytochrome P450 enzymes?
 a. CYP 3A4
 b. CYP 2D6
 c. CYP 2C9
 d. None of the above

Evaluation of CE

Drug Topics is conducting an evaluation of this CE article. Please ✓ box that best reflects your opinion of the evaluation questions. Please keep this evaluation attached to your answer form.

	Strongly Agree	Agree	Disagree	Strongly Disagree
1. The program objectives were met.				
2. The program content was useful and relevant.				
3. The program was educational and not promotional.				
4. The program was fair, objective, balanced, and of scientific rigor.				
5. The program will help me in my practice.				

2006 CEU CREDIT REQUEST

To obtain immediate CE credit, take the test on-line at www.drugtopics.com. Just click on the "Continuing Education" box on the *Drug Topics* home page, which will take you to the CE site. Log in, find and click on this lesson, and follow the three simple steps. Test results will be displayed immediately and you can print the certificate showing your earned CE credits.

ANSWER FORM

NEW DRUG UPDATE 2005—Part 2

FEBRUARY 20, 2006 012-999-06-016-H01

Test questions start on preceding page

- | | | | | |
|-----------------------|-----------------------|------------------------|------------------------|------------------------|
| 1. a. b. c. d. | 5. a. b. c. d. | 9. a. b. c. d. | 13. a. b. c. d. | 17. a. b. c. d. |
| 2. a. b. c. d. | 6. a. b. c. d. | 10. a. b. c. d. | 14. a. b. c. d. | 18. a. b. c. d. |
| 3. a. b. | 7. a. b. c. d. | 11. a. b. c. d. | 15. a. b. c. d. | 19. a. b. |
| 4. a. b. c. d. | 8. a. b. c. d. | 12. a. b. c. d. | 16. a. b. c. d. | 20. a. b. c. d. |

No longer valid for CE credit after 2/29/08

- Amount enclosed:** \$6.00 for this lesson
 \$54.00 for any 12 lessons you take over the next year, starting from the date you sign up
 Already series-enrolled for 2006

Submit your check (payable to The University of Florida) and form to:
 University of Florida College of Pharmacy, P.O. Box 100482, Gainesville, FL 32610

E-mail address: continuinged@cop.ufl.edu
 Fees not refundable or transferable

For questions concerning PRINT CEs, call (352) 273-6275.
For questions concerning ON-LINE CEs, call (866) 261-3558.

**Are you
employed
by a chain?
If so,
which one?**

REGISTRANT INFORMATION

Name:

(Last)

(First)

(M.I.)

Phone

Address:

(Street)

E-mail address:

City:

State:

Zip:

ATTENTION FLORIDA PHARMACISTS: The State of Florida has changed to a new record maintenance system for all continuing education, using a private company, **cebroker.com**. The University of Florida is registered with the Florida Board of Pharmacy as a Provider, and will report continuing education records for all pharmacists who are registered in Florida.

Please provide your license number _____