

New drug update 2005— Part 1



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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 lesson reviews the new molecular entities (NMEs) approved by the Food & Drug Administration in 2005. The FDA reports that 20 NMEs were cleared last year. This compares with 31 NMEs in 2004. Some of the most noteworthy 2005 NMEs that received the green light include the first in a new class of agents called incretin mimetics derived from the venom of the Gila monster, a synthetic human amylin analog/glucose metabolism regulator for adjunct treatment of Type 1 and Type 2 diabetes patients, and the first in a new class of protease inhibitors (PIs) called nonpeptidic PIs.

GOAL

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

CREDIT

This lesson provides **three** 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 discussion with patients 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.

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Here's a blow-by-blow account of 10 of the 20 NMEs. Part 2, which will run in the next issue, will cover the rest.

DEFERASIROX (Novartis)

Exjade FDA rating: 1-PO (P = priority review;
0 = orphan drug)

Indications: Deferasirox is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients two years of age and older. It is the first orally administered medication to be approved for this indication. According to Novartis, availability of the oral formulation is expected to improve compliance with iron chelation therapy in patients unwilling to undergo deferoxamine (Desferal) subcutaneous (SC) infusions lasting eight to 12 hours per night, on five to seven nights per week.

Pharmacokinetics: Deferasirox is absorbed following oral administration with median times to maximum plasma concentration (T_{max}) of about 90 minutes to four hours. The bioavailability (AUC) of deferasirox tablets for oral suspension is 70% compared with an IV dose.

Glucuronidation is the main metabolic pathway for deferasirox, with subsequent biliary excretion. Deconjugation of glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur. No evidence for induction or inhibition of enzymes at therapeutic doses has been observed. Deferasirox and metabolites are primarily excreted in the feces. Renal excretion of deferasirox and metabolites is minimal. The mean elimination half-life ranged from eight to 16 hours following oral administration.

Precautions: Deferasirox-treated patients experienced dose-dependent increases in serum creatinine. These increases occurred in about one-third of deferasirox-treated patients. Most of the creatinine elevations remained within normal range. Serum creatinine should be assessed before initiating therapy and should be monitored monthly thereafter to determine whether dose modification or discontinuation is necessary. Liver function should be monitored monthly, and if there is an unexplained, persistent, or progressive increase in serum transaminase levels, deferasirox should be interrupted or discontinued. Also, auditory and ocular disturbances have been reported with deferasirox therapy and monitoring is recommended.

Drug interactions: The concomitant administration of deferasirox and aluminum-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminum than for iron,

deferasirox should not be taken with aluminum-containing antacid preparations.

Deferasirox should not be combined with other iron chelator therapies as the safety of such combinations has not been established.

Adverse effects: The most frequently reported adverse events were transient in nature and included mild to moderate nausea, vomiting, diarrhea, abdominal pain, skin rash, and dose-dependent increases in serum creatinine. As with deferoxamine injection, deferasirox was associated with a low incidence of ocular and auditory disturbances.

Dosage and availability: The recommended initial daily dose of deferasirox is 20 mg/kg body weight. After initial therapy, it is recommended that serum ferritin be monitored every month and the dose of deferasirox adjusted if necessary every three to six months based on serum ferritin trends. Doses (mg/kg) should be calculated to the nearest whole tablet. Dose adjustments should be made in steps of 5 or 10 mg/kg and should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). If the serum ferritin falls consistently below 500 mcg per liter, consideration should be given to temporarily interrupting therapy with deferasirox. Doses of deferasirox should not exceed 30 mg/kg per day since there is limited experience with doses above this level.

Deferasirox should be taken on an empty stomach 30 minutes before eating.

Deferasirox is available as tablets for oral suspension in the following strengths: 125 mg, 250 mg, and 500 mg. Deferasirox tablets for oral suspension can be dispersed in water, orange juice, or apple juice.

Patient counseling: Deferasirox should be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day. Tablets should not be chewed or swallowed whole. Deferasirox should not be taken with aluminum-containing antacid products. Tablets should be completely dispersed by stirring in water, orange juice, or apple juice until a fine suspension is obtained. Doses of <1 gm should be dispersed in 3.5 oz. of liquid and doses of >1 gm in 7 oz. of liquid. After swallowing the suspension, any residue should be resuspended in a small volume of liquid and swallowed.

ENTECAVIR (Bristol-Myers Squibb) Baraclude FDA rating: 1-P

Indications: Entecavir is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with evidence of active viral replication and either evidence

of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

Pharmacokinetics: Entecavir is administered orally as a tablet or oral solution. The oral solution is 100% bioavailable relative to the tablet, and these two dosage forms can be used interchangeably. Oral absorption of entecavir is affected by food; food delays absorption, decreases maximum serum concentration (C_{max}) by 44% to 46%, and decreases AUC concentrations by 18% to 20%. Entecavir should be administered on an empty stomach at least two hours before or after a meal. Steady-state concentrations are achieved after six to 10 days of once-daily dosing.

Entecavir is not a substrate, inhibitor, or inducer of the CYP 450 enzyme system. Entecavir is predominately eliminated by the kidney with 62% to 73% of the dose recovered as unchanged drug in the urine.

Precautions: There is a possibility of hepatitis exacerbation when discontinuing therapy. Hepatic function should be monitored closely for at least several months after discontinuing antihepatitis therapy.

Dosage adjustment of entecavir is recommended for patients with a creatinine clearance <50 ml/min, including patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). The safety and efficacy of entecavir in liver transplant recipients are unknown.

Drug interactions: Entecavir is eliminated by active tubular secretion, but, according to the manufacturer, the pharmacokinetics of entecavir or the coadministered drug were not altered when given with adefovir (Hepsera), lamivudine (Epivir), and tenofovir (Viread).

Adverse effects: The reported adverse events with entecavir were similar to adverse events with lamivudine with regard to type and frequency. Reported ALT concentrations were lower for entecavir than they were for lamivudine-treated patients. Other laboratory abnormalities include elevated amylase levels, elevated lipase concentrations, hyperbilirubinemia, fasting hyperglycemia, glycosuria, and hematuria.

Dosage and availability: The recommended dose of entecavir for chronic HBV infection in nucleoside-treatment-naive adults and adolescents 16 years of age and older is 0.5 mg once daily. The recommended dose of entecavir in adults and adolescents (≥ 16 years of age) with a history of hepatitis B viremia while receiving lamivudine or known lamivudine-resistance mutations is 1 mg once daily.

Patients should be advised to take entecavir on an empty stomach (at least two hours after a meal and two

hours before the next meal). The oral solution contains 0.05 mg of entecavir per milliliter.

Dosage adjustment is recommended for patients with creatinine clearance <50 ml/min, including patients on hemodialysis or CAPD. The package insert contains a handy table for deciding the proper dose in patients with renal impairment.

Patient counseling: Patients should discuss any new symptoms or concurrent medications with their physician. Patients should be informed that deterioration of liver disease may occur in some cases if treatment is discontinued, and that they should discuss any change in regimen with their physician. Patients should be advised that treatment with entecavir has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination.

EXENATIDE (Amylin)
Byetta FDA rating: 1-S (S = standard review)

Indications: Exenatide is the first in a new class of agents called incretin mimetics. Incretins are endogenous compounds, such as glucagon-like peptide-1 (GLP-1), that improve glycemic control once released into the circulation via the gut. Exenatide is indicated as an adjunctive therapy to improve glycemic control in patients with Type 2 diabetes mellitus who have not achieved adequate control on metformin, a sulfonyleurea, or a combination of metformin and a sulfonyleurea. Exenatide is a 39-amino acid GLP-1 agonist isolated from the salivary gland venom of the lizard *Heloderma suspectum* (Gila monster). Exenatide significantly reduces glycosylated hemoglobin (HbA1c) concentrations by 0.4% to 0.9%. Therefore, a larger number of patients achieve the American Diabetes Association's recommended goal of <7%.

Pharmacology and pharmacokinetics: Exenatide binds and activates the human GLP-1 receptor site in vitro. Occupation of the GLP-1 receptor site by exenatide results in an increase in both glucose-dependent synthesis of insulin and in vivo secretion of insulin from pancreatic beta cells in the presence of elevated glucose. Increased synthesis and release of insulin occurs via mechanisms involving cyclic AMP and/or other intracellular signaling pathways.

Exenatide suppresses glucagon secretion, slows gastric emptying, reduces food intake, and promotes β -cell proliferation. The agent leads to a release of insulin only in the presence of elevated glucose concentrations. Insulin secretion subsides as euglycemia occurs. Exenatide slows gastric emptying, thereby

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New molecular entities of 2005			
Generic name	Brand name	Manufacturer	Indication
Abatacept	Orencia	Bristol-Myers Squibb	Treatment of adults with moderate to severe rheumatoid arthritis
Conivaptan hydrochloride	Vaprisol	Astellas	Treatment of euvolemic hyponatremia in hospitalized patients
Deferasirox	Exjade	Novartis	Treatment of chronic iron overload due to blood transfusions
Entecavir	Baraclude	Bristol-Myers Squibb	Treatment of chronic HBV infection in adults
Exenatide	Byetta	Amylin Pharmaceuticals	Indicated to improve glycemic control in patients with Type 2 diabetes
Galsulfase	Naglazyme	BioMarin	Treatment of the genetic disease mucopolysaccharidosis type VI
Hyaluronidase	Hydase	PrimaPharm	An adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and for improving resorption of radiopaque agents
Hyaluronidase	Hylenex	Halozyme	An adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and for improving resorption of radiopaque agents
Insulin detemir	Levemir	Novo Nordisk	Indicated for patients with Type 1 or Type 2 diabetes who require basal (long-acting) insulin
Lenalidomide	Revlimid	Celgene	Treatment of transfusion-dependent anemia in a subgroup of patients with myelodysplastic syndrome
Mecasermin (rDNA origin)	Increlex	Tercica	Treatment of 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
Mecasermin rinfabate (rDNA origin)	iPlex	Insmed	Treatment of growth failure in children with severe primary IGFD or with GH gene deletion who have developed neutralizing antibodies to GH
Micafungin sodium	Mycamine	Fujisawa	Treatment of esophageal candidiasis and for the prophylaxis of <i>Candida</i> infections in patients undergoing hematopoietic stem cell transplantation.
Nelarabine	Arranon	GlaxoSmithKline	Treatment of T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma
Nepafenac	Nevanac	Alcon	Treatment of pain and inflammation associated with cataract surgery
Pramlintide acetate	Symlin	Amylin Pharmaceuticals	Adjunct treatment in Type 1 and Type 2 diabetes
Ramelteon	Rozerem	Takeda	Treatment of insomnia
Sorafenib	Nexavar	Bayer Pharmaceuticals	Treatment of patients with advanced renal cell carcinoma
Tigecycline	Tygacil	Wyeth Pharmaceuticals	Indicated for the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections
Tipranavir	Aptivus	Boehringer Ingelheim	Indicated for combination antiretroviral treatment of HIV-1

Adapted from the FDA at www.fda.gov/cder/rdmt/ndaaps05cy.htm

reducing the rate at which meal-derived glucose appears in the circulation. Exenatide does not increase insulin activity in nondiabetics.

Exenatide is given via SC administration. It reaches peak plasma concentrations in roughly two hours. Similar absorption is achieved with SC administration of exenatide in the abdomen, thigh, or arm. Exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean terminal half-life is 2.4 hours.

Precautions: Exenatide should not be used in patients with Type 1 diabetes or for the treatment of diabetic ketoacidosis. Exenatide is not a substitute for insulin in insulin-requiring patients. Exenatide is not recommended for patients with end-stage renal disease or patients with creatinine clearance of <30 ml/min. Exenatide is also not recommended for patients with severe gastrointestinal (GI) disease.

Drug interactions: Exenatide slows gastric emptying, which may reduce the rate and/or extent of absorption of orally administered drugs. Repeat doses of exenatide (10 mcg SC twice daily) decreased the C_{max} of digoxin (0.25 mg p.o. daily) by 17% and delayed T_{max} by roughly 2.5 hours. Overall steady state AUC of digoxin was not altered.

Lovastatin AUC and C_{max} were decreased approximately 40% and 28%, respectively, and T_{max} was delayed about four hours when exenatide (10 mcg SC twice daily) was administered concomitantly with a single dose of lovastatin (40 mg p.o.) compared with lovastatin administered alone, but the risk for lipid profile alterations is minimal.

Adverse effects: Hypoglycemia has occurred in patients receiving sulfonylureas plus exenatide (with or without metformin). In clinical trials research, nausea/vomiting occurred at a high rate overall in the exenatide group (44%/13% vs. 18%/4% placebo).

Dosage and availability: Therapy should be initiated at 5 mcg per dose twice daily at any time within the 60-minute period before the morning and evening meals. Dose should be administered as a SC injection in the thigh, abdomen, or upper arm. Exenatide should not be administered after a meal. Doses can be increased to 10 mcg twice daily after one month of therapy, if necessary.

Exenatide is supplied as a sterile solution for SC injection containing 250 mcg/ml exenatide. The following packages are available: 5 mcg per dose, 60 doses, 1.2-ml prefilled pen and 10 mcg per dose, 60 doses, 2.4-ml prefilled pen.

Patient counseling: The risk of hypoglycemia is increased when exenatide is used in combination with an

agent that induces hypoglycemia, such as a sulfonylurea. The symptoms, treatment, and conditions that predispose development of hypoglycemia should be explained to the patient. While the patient's usual instructions for hypoglycemia management do not need to be changed, these instructions should be reviewed and reinforced when initiating exenatide therapy, particularly when concomitantly administered with a sulfonylurea.

Patients should also be fully informed about self-management practices, including the importance of proper storage of exenatide, injection technique, timing of dosage of exenatide as well as concomitant oral drugs, adherence to meal planning, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications.

Patients should be advised that treatment with exenatide may result in a reduction in appetite, food intake, and/or body weight, and that there is no need to modify the dosing regimen because of such effects. Treatment with exenatide may also result in nausea, particularly upon initiation of therapy. Exenatide should be stored refrigerated at 36°F to 46°F (2°C to 8°C), protected from light. The pen should be discarded 30 days after first use, even if some drug remains in it. Do not freeze. Do not use exenatide if it has been frozen.

**HYALURONIDASE (PrimaPharm)
Hydase FDA rating: 1-P**

Indications: Hyaluronidase is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in SC urography for improving resorption of radiopaque agents. Although previously marketed, hyaluronidase was not available in the United States for several years. In the past, it was most commonly used in combination with local anesthetics in ophthalmic surgery.

Pharmacology and pharmacokinetics: The Hydase brand of hyaluronidase is a preparation of purified bovine testicular hyaluronidase, a protein enzyme. The exact chemical structure of this enzyme is unknown. However, the amino acid sequence for the primary structure of the enzyme has been deduced from the sequence of purified peptides. Hyaluronidase is a spreading or diffusing substance that modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid, a polysaccharide found in the intercellular ground substance of connective tissue and of certain specialized tissues, such as the umbilical cord and vitreous humor. Hyaluronidase hydrolyzes hyaluronic acid by splitting

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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.

The rate of diffusion is proportionate to the amount of enzyme, and the extent is proportionate to the volume of solution.

Precautions: When considering the administration of any other drug with hyaluronidase, it is recommended that appropriate references first be consulted to determine the usual precautions for the use of the other drug; e.g., when epinephrine is injected along with hyaluronidase, the precautions for the use of epinephrine in cardiovascular disease, thyroid disease, diabetes, digital nerve block, ischemia of the fingers and toes, and so on should be observed.

The physician should be advised not to inject hyaluronidase into or around an infected or acutely inflamed area because of the danger of spreading a localized infection. Hyaluronidase should not be used to reduce the swelling of bites or stings. The agent should not be applied directly to the cornea. Hyaluronidase should not be used for IV injections because the enzyme is rapidly inactivated.

Drug interactions: When hyaluronidase is added to a local anesthetic agent, it hastens the onset of analgesia and tends to reduce the swelling caused by local infiltration, but the wider spread of the local anesthetic solution increases its absorption. This shortens its duration of action and tends to increase the incidence of systemic reaction.

Patients receiving large doses of salicylates, cortisone, ACTH (adrenocorticotrophic hormone), estrogens, or antihistamines may require larger amounts of hyaluronidase for equivalent dispersing effect, since these drugs apparently render tissues partly resistant to the action of hyaluronidase.

Furosemide, the benzodiazepines, and phenytoin have been found to be incompatible with hyaluronidase.

Adverse effects: The most frequently reported adverse experiences have been local injection site reactions. Hyaluronidase has been reported to enhance the adverse events associated with coadministered drug products. Edema has been reported most frequently in association with hypodermoclysis. Allergic reactions (urticaria, angioedema) have been reported in less than 0.1% of patients receiving hyaluronidase. Anaphylactic-like reactions following retrobulbar block or IV injections have occurred, but rarely.

Dosage and availability: Absorption and dispersion

of other injected drugs may be enhanced by adding 50-300 Units, usually 150 U hyaluronidase, to the injection solution. Hydase (hyaluronidase injection) is supplied as a sterile, colorless, odorless, ready-to-use solution. Each vial contains 150 USP units of hyaluronidase per ml.

Patient counseling: Typically, this medication is used by or under the direct supervision of a physician. Discontinue hyaluronidase injection if sensitization occurs.

INSULIN DETEMIR (Novo Nordisk) Levemir FDA rating: 1-S

Indications: Levemir is indicated for once- or twice-daily SC administration in the treatment of pediatric patients with Type 1 diabetes or adults with Type 2 diabetes who require basal (long-acting) insulin for the control of hyperglycemia.

Pharmacology and pharmacokinetics: Insulin detemir is a long-acting basal insulin analog, with up to 24 hours' duration of action, produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae* followed by chemical modification.

Insulin detemir has been associated with a flatter time-action profile than NPH insulin, with peak plasma concentrations reached in six to eight hours of SC injection. For doses ranging from 0.2 to 0.4 Units/kg, more than 50% of the maximum effect of insulin detemir is exerted from three to four hours to approximately 14 hours after SC administration. Insulin detemir displays a relatively linear and dose-proportional pharmacokinetic profile, providing metabolic effect for up to 24 hours. After SC injection of insulin detemir in healthy subjects and in patients with diabetes, insulin detemir serum concentrations indicated a slower, more prolonged absorption over 24 hours in comparison with NPH human insulin.

The absolute bioavailability of insulin detemir is approximately 60%.

Precautions: The precautions for using this form of insulin are similar to those for the other forms of the drug. Glucose monitoring is recommended for all patients with diabetes. Insulin detemir is not to be used in insulin infusion pumps.

Drug interactions: Insulin detemir is 98% to 99% bound to plasma albumin. It does not appear that insulin detemir has any clinically significant drug interactions with other drugs known to be highly bound to albumin (i.e., sulfonyleureas, aspirin, valproic acid, warfarin, phenylbutazone, and diazepam).

Adverse effects: Hypoglycemia is the most common adverse effect of insulin therapy, including insulin

detemir. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.

Dosage and availability: Insulin detemir is administered by intermittent SC injection only. For once-daily dosing, insulin detemir should be administered with an evening meal or at bedtime. For twice-daily dosing, the second dose (evening dose) can be given with the evening meal or 12 hours after the morning dose.

Patient counseling: Insulin detemir should be used only if the solution appears clear and colorless with no visible particles. Patients should be informed about potential risks and advantages of insulin detemir therapy, including the possible side effects. Patients should be offered continued education and advice on insulin therapies, injection technique, lifestyle management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dosage, instruction for use of injection devices, and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve effective glycemic control to avoid both hyperglycemia and hypoglycemia.

MECASERMIN of rDNA Origin (Tercica)

Increlex FDA rating: 1-PO

Indications: Mecasermin is indicated for the long-term treatment of growth failure in children with severe primary insulin-like growth factor-1 (IGF-1) deficiency (primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. Mecasermin is not intended for use in subjects with secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

Pharmacology and pharmacokinetics: Mecasermin (rh-IGF-1) is a recombinant product, manufactured by genetic modification, to be identical to that of endogenous human insulin-like growth factor-1 (IGF-1). It is a single-chain polypeptide consisting of 70 amino acids; roughly 50% of its amino acid sequence is homologous with insulin. IGF-1 is the primary mediator of growth hormone and has many actions in the body including the promotion of skeletal, organ, and other tissue growth, the suppression of hepatic glucose production, the inhibition of insulin secretion, and the maintenance and regeneration of the nervous system.

While the bioavailability of rhIGF-1 after SC administration in healthy subjects has been reported to be

close to 100%, the absolute bioavailability of mecasermin given subcutaneously to subjects with primary IGFD has not been determined.

The mean terminal half-life after single SC administration of 0.12 mg/kg mecasermin in pediatric subjects with severe primary IGFD is estimated to be 5.8 hours.

Precautions: Treatment with mecasermin should be directed by physicians who are experienced in the diagnosis and management of patients with growth disorders. Mecasermin has not been studied in children less than two years of age or in adults. It should be administered shortly before or after a meal or snack, because it has insulin-like hypoglycemic effects. Special attention should be paid to small children because their oral intake may not be consistent. Patients should avoid engaging in any high-risk activities (e.g., driving) within two to three hours after dosing, particularly at the initiation of mecasermin treatment, until a well-tolerated dose of mecasermin has been established.

Drug interactions: Drug interaction studies have not been performed with mecasermin. Caution should be used in combining mecasermin with antidiabetic agents because the hypoglycemic effect induced by IGF-1 activity may be exacerbated. Use caution in concomitant use of mecasermin and recombinant growth hormone (rh-GH). Both agents are used in the treatment of growth disorders and share feedback and pathway systems. Use caution in combining mecasermin, recombinant, rh-IGF-1 with psychostimulant agents, including methylphenidate, dexamethylphenidate, amphetamine, dextroamphetamine, and methamphetamine, used as adjunctive treatment in patients with attention-deficit disorder (ADD), attention-deficit hyperactivity disorder (ADHD), and narcolepsy.

Adverse effects: As with all protein pharmaceuticals, some patients may develop antibodies to mecasermin. In clinical trials, anti-IGF-1 antibodies were present at one or more of the periodic assessments in 14 of 23 children with primary IGFD treated for two years. However, no clinical consequences of these antibodies were observed (e.g., allergic reactions or attenuation of growth).

Hypoglycemia was reported by 30 subjects (42%) at least once during their course of therapy. Most cases of hypoglycemia were mild or moderate in severity. Five subjects had severe hypoglycemia (requiring assistance and treatment) on one or more occasions, and four subjects experienced hypoglycemic seizures/loss of consciousness on one or more occasions. The frequency of hypoglycemia was highest in the first month of treatment, and episodes were more frequent in younger children. Symptomatic hypoglycemia was generally avoid-

ed when a meal or snack was consumed either shortly (i.e., 20 minutes) before or after the administration of mecasecmin.

Tonsillar hypertrophy was noted in 11 (15%) subjects in the first one to two years of therapy, with lesser tonsillar growth in subsequent years.

Mild elevations in the serum AST and LDH were found in a significant proportion of patients before and during treatment, and no rise in levels of these serum enzymes led to treatment discontinuation. Echocardiographic evidence of cardiomegaly/valvulopathy was observed in a few individuals without associated clinical symptoms. Because of underlying disease and the lack of control group, the relation of the cardiac changes to drug treatment cannot be assessed. Thickening of the soft tissues of the face was observed in several patients and should be monitored during mecasecmin treatment.

Dosage and availability: The dosage of mecasecmin should be individualized for each patient. The recommended starting dose of mecasecmin is 0.04 to 0.08 mg/kg (40 to 80 mcg/kg) twice daily by SC injection. If well-tolerated for at least one week, the dose may be increased by 0.04 mg/kg per dose, to the maximum dose of 0.12 mg/kg given twice daily. Doses greater than 0.12 mg/kg given twice daily have not been evaluated in children with primary IGFD and, due to potential hypoglycemic effects, should not be used. If hypoglycemia occurs with recommended doses, despite adequate food intake, the dose should be reduced. Mecastecmin should be administered shortly before or after (\pm 20 minutes) a meal or snack. If the patient is unable to eat shortly before or after a dose for any reason, that dose of mecasecmin should be withheld. Subsequent doses of mecasecmin should never be increased to make up for one or more omitted dose. Mecastecmin injection sites should be rotated to a different site with each injection.

Mecastecmin is supplied as a 10 mg/ml sterile solution in multiple-dose glass vials (40 mg/vial).

Patient counseling: Patients and/or their parents should be instructed in the safe administration of mecasecmin. Mecastecmin should be given shortly before or after (20 minutes on either side of) a meal or snack. It is important not to administer mecasecmin when a meal or snack is omitted. The dose of mecasecmin should never be increased to make up for one or more omitted doses. Mecastecmin therapy should be initiated at a low dose, and the dose should be increased only if no hypoglycemia episodes have occurred after at least seven days of dosing. If severe hypoglycemia or persistent hypoglycemia occurs on treatment despite adequate

food intake, mecasecmin dose reduction should be considered. Providers should educate patients and caregivers on how to recognize the signs and symptoms of hypoglycemia.

When unopened, vials of mecasecmin are stable when refrigerated. Avoid freezing the vials of mecasecmin. Protect from direct light. Expiration dates are stated on the labels. After opening, vials of mecasecmin are stable for 30 days after initial vial entry when stored at 2°C to 8°C (35°F to 46°F). Vial contents should be clear without particulate matter. If the solution is cloudy or contains particulate matter, the contents must not be injected. Remaining unused material should be discarded.

MICAFUNGIN SODIUM (Fujisawa) Mycamine FDA rating: 1-P

Indications: Mycamine is indicated for the treatment of esophageal candidiasis and for the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation. The efficacy of micafungin for the treatment of infections caused by fungi other than *Candida* has not been established.

Pharmacology and pharmacokinetics: Micafungin (also known as FK463) is an IV antifungal agent. Both caspofungin and micafungin are in a new class of antifungals called the echinocandins, which have fewer side effects and less propensity for drug interactions as compared with other available antifungal agents. Micafungin, a semisynthetic lipopeptide, is derived from a fermentation product of *Coleophoma empetri*.

Micafungin inhibits the synthesis of β -(1,3)-D-glucan. Micafungin has shown fungicidal activity against *Candida spp.*, but activity against *Aspergillus* requires further investigation. Cross-resistance with amphotericin B or the azole antifungals has not been observed. The potential for drug resistance development is unknown. Standardized susceptibility testing methods for β -(1,3)-D-glucans are not currently available.

Precautions: Abnormalities in liver function tests (LFTs) have been reported in healthy volunteers and patients treated with micafungin. Some patients with underlying illness simultaneously receiving micafungin and other medications developed hepatic abnormalities, hepatic dysfunction, hepatitis, or worsening hepatic failure. If abnormal LFTs should develop, those patients should be monitored for worsening hepatic function to determine if the benefits still outweighs the risk of continuing treatment with micafungin.

Elevated blood urea nitrogen (BUN) and creatinine levels have been reported with use of micafungin,

including isolated cases of renal dysfunction and acute renal failure. Patients who develop abnormal renal function tests, should be monitored for worsening renal function.

Isolated cases of hemolysis and hemolytic anemia have been reported during micafungin therapy. Patients who develop evidence of these conditions should be monitored closely and evaluated for the risk/benefit of continuing treatment.

Drug interactions: A total of 11 clinical drug-drug interaction studies were conducted in healthy volunteers to evaluate the potential for interaction between micafungin and mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, and rifampin. In these studies, no interaction that altered the pharmacokinetics of micafungin was observed. There was no effect of a single dose or multiple doses of micafungin on mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, and fluconazole pharmacokinetics.

Sirolimus AUC was increased by 21% with no effect on C_{max} in the presence of steady-state micafungin compared with sirolimus alone. Nifedipine AUC and C_{max} were increased by 18% and 42%, respectively, in the presence of steady-state micafungin compared with nifedipine alone. Patients receiving sirolimus or nifedipine in combination with micafungin should be monitored for sirolimus or nifedipine toxicity, and sirolimus or nifedipine dosage should be reduced if necessary. Micafungin is not an inhibitor of P-glycoprotein and, therefore, would not be expected to alter P-glycoprotein-mediated drug transport activity.

Adverse effects: Possible histamine-mediated symptoms have been reported with micafungin, including rash, pruritus, facial swelling, and vasodilatation. Injection site reactions, including phlebitis and thrombophlebitis have been reported, at doses of 50-150 mg/day. These events tended to occur more often in patients receiving the drug via peripheral IV administration.

Dosage and availability: The recommended dosage of micafungin for the treatment of esophageal candidiasis is 150 mg per day and 50 mg per day for the prophylaxis of *Candida* infections in hematopoietic stem cell transplant recipients. During clinical trials, the mean duration of successful therapy was 15 days and 19 days, respectively.

Micafungin is available in cartons of 10 individually packaged 50-mg single-use vials. Unopened vials must be stored at room temperature.

Patient counseling: Before taking micafungin, patients should inform their doctor or pharmacist if they are allergic to it or if they have any other allergies. Before

using this medication, patients should reveal to their doctor or pharmacist pertinent medical history, such as liver disease, kidney disease, or blood disorders (e.g., anemia, decreased bone marrow function).

NELARABINE (GlaxoSmithKline)
Arranon FDA rating: 1-PO

Indications: Nelarabine is a purine analog antimetabolite indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

Pharmacology and pharmacokinetics: Nelarabine is a pro-drug of the deoxyguanosine analog 9- β -D-arabinofuranosylguanine (ara-G). Nelarabine is demethylated by adenosine deaminase (ADA) to ara-G, mono-phosphorylated by deoxyguanosine kinase and deoxycytidine kinase, and subsequently converted to the active 5'-triphosphate, ara-GTP. Accumulation of ara-GTP in leukemic blasts allows for incorporation into DNA, leading to inhibition of DNA synthesis and cell death. Other mechanisms may contribute to the cytotoxic and systemic toxicity of nelarabine.

Pharmacokinetic studies in adult patients with refractory leukemia or lymphoma have demonstrated that nelarabine and ara-G are rapidly eliminated from plasma with a half-life of approximately 30 minutes and three hours, respectively, after a 1,500 mg/m² nelarabine dose.

Plasma ara-G C_{max} values generally occurred at the end of the nelarabine infusion and were generally higher than nelarabine C_{max} values, suggesting rapid and extensive conversion of nelarabine to ara-G.

Nelarabine and ara-G are partially eliminated by the kidneys. Mean urinary excretion of nelarabine and ara-G was 6.6 \pm 4.7% and 27 \pm 15% of the administered dose, respectively, in 28 adult patients over the 24 hours after nelarabine infusion on day one.

Precautions: Neurotoxicity is the dose-limiting toxicity of nelarabine. Patients should be closely monitored for confusion, somnolence, convulsions, ataxia, paresthesia, and hypoesthesia. Patients previously treated with intrathecal chemotherapy or craniospinal radiation are at increased risk for these neurological side effects.

Leukopenia, thrombocytopenia, anemia, and neutropenia, including febrile neutropenia, have been associated with nelarabine therapy. Complete blood counts including platelets should be monitored regularly.

Patients receiving nelarabine should receive IV hydration according to standard medical practice for the management of hyperuricemia in patients at risk for tumor lysis syndrome. Consideration should be given to the use of allopurinol in patients at risk of hyperuricemia. Administration of live vaccines to immunocompromised patients should be avoided.

Drug interactions: There are no reported significant interaction with nelarabine and ara-G. They did not significantly inhibit the activities of the human hepatic cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 in vitro at concentrations of nelarabine and ara-G up to 100 micromolars.

Adverse effects: The most common adverse events in pediatric patients, regardless of causality, were hematologic disorders (anemia, leukopenia, neutropenia, and thrombocytopenia). Of the nonhematologic adverse events in pediatric patients, the most frequent events reported were headache, increased transaminase levels, decreased blood potassium, decreased blood albumin, increased blood bilirubin, and vomiting.

The most common adverse events in adults, regardless of causality, were fatigue; GI disorders (nausea, diarrhea, vomiting, and constipation); hematologic disorders (anemia, neutropenia, and thrombocytopenia); respiratory disorders (cough and dyspnea); nervous system disorders (somnolence and dizziness); and pyrexia.

Dosage and availability: Nelarabine is administered undiluted. The appropriate dose of nelarabine is transferred into polyvinylchloride (PVC) infusion bags or glass containers and administered as a two-hour infusion in adult patients and as a one-hour infusion in pediatric patients. Prior to administration, the pharmacist or nurse should inspect the drug product visually for particulate matter and discoloration.

The recommended adult dose of nelarabine is 1,500 mg/m² administered intravenously over two hours on days one, three, and five, repeated every 21 days. The recommended pediatric dose of nelarabine is 650 mg/m² administered intravenously over one hour daily for five consecutive days, repeated every 21 days. The recommended duration of treatment for adult and pediatric patients has not been clearly established. In clinical trials, treatment was generally continued until there was evidence of disease progression, the patient experienced unacceptable toxicity, the patient became a candidate for bone marrow transplant, or the patient no longer continued to benefit from treatment.

Nelarabine injection is supplied as a clear, colorless, sterile solution. Each vial contains 250 mg of nelarabine (5 mg nelarabine per ml) and the inactive ingredient sodium chloride (4.5 mg per ml) in 50 ml Water for Injection, USP.

Patient counseling: Since patients receiving nelarabine therapy may experience somnolence, they should be cautioned about operating hazardous machinery, including automobiles. Patients should be instructed to contact their physician if they experience new or worsening symptoms of peripheral neuropathy. These signs and symptoms include: tingling or numbness in fingers, hands, toes, or feet; difficulty with the fine motor coordination tasks such as buttoning clothing; unsteadiness while walking; weakness arising from a low chair; weakness in climbing stairs; and increased tripping while walking over uneven surfaces.

Patients should be instructed that seizures have been known to occur in patients who receive nelarabine. If a seizure occurs, the physician administering nelarabine should be promptly informed. Patients who develop fever or signs of infection while on therapy should notify their physician promptly.

NEPAFENAC (Alcon)
Nevanac FDA rating: 1-P

Indications: Nepafenac ophthalmic suspension is a topical nonsteroidal anti-inflammatory (NSAID) pro-drug for the treatment of the pain and inflammation associated with cataract surgery. Nepafenac is the first ophthalmic NSAID pro-drug.

Pharmacology and pharmacokinetics: The pro-drug structure of nepafenac allows for rapid penetration to the cornea and distribution to target sites, while minimizing surface accumulation and reducing ocular surface complications.

Following ophthalmic administration, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, an NSAID. The anti-inflammatory and analgesic properties of amfenac are mediated through inhibition of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production. The prostaglandins play a role in the miotic response produced during and after ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms. With ophthalmic administration, NSAIDs inhibit the synthesis of prostaglandins in the iris, ciliary body, and conjunctiva and, thus, work to prevent manifestations of ocular inflammation and reduce pain.

Although the drug is applied topically, quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects given nepafenac ophthalmic solution three times daily. The clinical significance of the systemic absorption of nepafenac after ophthalmic administration is unknown.

Precautions: Topical NSAIDs, including nepafenac, may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation. These events may threaten the sight. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including nepafenac and should be closely monitored for corneal health.

Drug interactions: There are no reported drug-drug interactions with nepafenac.

Adverse effects: The most frequently reported ocular adverse events in clinical studies with nepafenac following cataract surgery, reported in 5% to 10% of patients, included capsular opacity, visual impairment (decreased visual acuity), foreign body sensation, ocular hypertension, and sticky sensation. Approximately 1% to 5% of patients experienced conjunctival or corneal edema, xerophthalmia, lid margin crusting, ocular irritation, conjunctival hyperemia, ocular pain, ocular pruritus, photophobia, lacrimation (tearing), and vitreous detachment. Some of these events may have been a result of the cataract surgical procedure as opposed to nepafenac administration.

Dosage and availability: Shake well before use. For adults, elderly, adolescents, and children >10, administer one drop into the affected eye or eyes three times a day beginning one day prior to cataract surgery, continued on the day of surgery and through the first two weeks of the postoperative period.

Nepafenac is available in a 0.1% ophthalmic suspension. The suspension is a translucent, yellow color. It comes in 3 ml of solution in a 4-ml bottle.

Patient counseling: Patients need to remove contact lenses before administering nepafenac ophthalmic suspension. Nepafenac ophthalmic suspension contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Also, contact lens removal is needed for drug penetration into the eye. Patients should wait about five minutes after nepafenac administration before reinserting contact lenses.

TIPRANAVIR (Boehringer Ingelheim) Aptivus FDA rating: 1-P

Indications: Tipranavir, coadministered with 200 mg of ritonavir, is indicated for combination antiretroviral treatment of HIV-1-infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

Pharmacology and pharmacokinetics: Tipranavir is the first in a new class of protease inhibitors (PIs) called nonpeptidic PIs. The nonpeptidic structure theoretically exhibits greater flexibility in conforming to HIV protease variants that are resistant to current PIs, and may also decrease the rate of development of resistance.

Precautions: New-onset diabetes, exacerbation of pre-existing diabetes, and hyperglycemia have been reported during postmarketing surveillance in patients receiving PIs. Dose-dependent hepatotoxicity was reported in 6% of tipranavir-treated patients in clinical trials and is the major safety concern of tipranavir. Patients with hepatitis or other hepatic disease appear to be at greater risk for continued hepatic impairment during tipranavir use. Due to hepatic safety concerns, and in an effort to evade widespread resistance, the use of tipranavir should be reserved as a salvage therapy for individuals who exhibit multiple PI viral mutations, have advanced disease, are treatment-experienced, and continue to show evidence of ongoing viral replication.

Tipranavir is contraindicated in patients with moderate and severe hepatic disease (Child-Pugh B or C).

Drug interactions: Tipranavir, coadministered with ritonavir at the recommended dose, is a net inhibitor of CYP3A4 hepatic enzymes; clinically significant drug interactions may occur with other CYP3A4 substrates. Co-administration of tipranavir and ritonavir with CYP3A4 and/or P-glycoprotein (Pgp) inducers may decrease tipranavir plasma concentrations; coadministration with Pgp inhibitors may increase tipranavir plasma concentrations; and coadministration with CYP3A4 inhibitors may not further increase tipranavir plasma concentrations.

The risk of myopathy, including rhabdomyolysis, may be increased when tipranavir and ritonavir are given in combination with most HMG-CoA reductase inhibitors.

Particular caution should be used when prescribing phosphodiesterase type 5 (PDE5) inhibitors to patients receiving tipranavir with ritonavir.

Pharmacists should consult the prescribing information for tipranavir for a complete list of clinically significant drug interactions.

Adverse effects: Dose-dependent hepatotoxicity, with elevated hepatic enzymes, has been the major safety

CONTINUING EDUCATION

concern with tipranavir. Liver function tests should be performed prior to initiating therapy and frequently throughout treatment. The administration of tipranavir, with ritonavir, has been associated with the development of hepatitis and hepatic decompensation, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications, so a causal relationship to tipranavir with ritonavir could not be established. Mild to moderate rash has been reported with tipranavir use.

Dosage and availability: Tipranavir (Aptivus) is supplied as 250-mg, pink, oblong, soft gelatin capsules imprinted in black with "TPV 250." The recommended dose is 500 mg (two 250-mg capsules), coadministered with 200 mg of ritonavir, twice daily. Tipranavir should be used in combination with an individualized anti-retroviral regimen and must be administered with low-dose ritonavir in order to attain appropriate concentrations and allow for twice-daily dosing.

Patient counseling: Because of the known hepatotoxicity with this drug, extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C coinfection, as these patients have an increased risk of hepatotoxicity. Patients should store unopened bottles of tipranavir capsules in a refrigerator at approximately 36°F to 46°F (2°C to 8°C). Once the bottle is opened, the contents must be used within 60 days. Patients should always take this medication with food. Advise patients that when their supply starts to run low, they should get more from their doctor or pharmacy. This is very important because the amount of virus in the blood may increase if the drug is stopped for even a short period of time. The HIV virus may develop resistance to tipranavir and become more difficult to treat. Patients should NEVER stop taking tipranavir or other HIV medicines without talking with their doctor.

References are available upon request.

TEST QUESTIONS

Write your answers on the answer form appearing on page 34 (photocopies of the answer form are acceptable) or on a separate sheet of paper. Mark the most appropriate answer.

1. Tipranavir is the first in a new class of protease inhibitors (PIs) called:
 - a. Non-peptidic PIs
 - b. Non-PIs
 - c. DNA gyrase inhibitors
 - d. Non-nuclease PIs
2. Tipranavir is contraindicated in patients with moderate and severe:
 - a. Renal disease
 - b. Congestive heart failure
 - c. Peripheral neuropathy
 - d. Hepatic disease
3. Proper use of tipranavir calls for it to be coadministered with:
 - a. Lamivudine
 - b. Ritonavir
 - c. Zidovudine
 - d. Falsimivir
4. Nelarabine is a pro-drug of the deoxyguanosine analog:
 - a. Methotrexate
 - b. Cyclophosphamide
 - c. Ara-G
 - d. Vidarabine
5. Patients at risk for tumor lysis syndrome who are receiving nelarabine should receive intravenous hydration according to standard medical practice for the management of:
 - a. Hypercalcemia
 - b. Hyperkalemia
 - c. Hyperuricemia
 - d. Gyperaldosteronism
6. The most common adverse events in pediatric patients taking nelarabine are:
 - a. Hematologic side effects
 - b. Hepatotoxicity
 - c. Peripheral neuropathy
 - d. Pulmonary fibrosis
7. Entecavir is a nucleoside analog used for the treatment of chronic:
 - a. Hepatitis B virus infection
 - b. Bone marrow infections
 - c. Skin and soft tissue infections
 - d. Middle ear infections
8. Dosage adjustment of entecavir is recommended for patients with:
 - a. Moderate and severe hepatic disease (Child-Pugh B or C)
 - b. Low-density lipoprotein (LDL) cholesterol above 200 mg/dl
 - c. Creatinine clearance <50 ml/min
 - d. Blood urea nitrogen (BUN) greater than 20 mg/dl
9. The pharmacokinetics of entecavir or the coadministered drug are altered when the drug is given with:
 - a. Adefovir
 - b. Lamivudine
 - c. Tenofovir
 - d. None of the above
10. Exenatide is the first in a new class of agents called:
 - a. Secretagogues
 - b. Polycyclic adenocyclase inhibitors
 - c. Incretin mimetics
 - d. Glycopolysaccharide analogs
11. Exenatide is a 39-amino acid glucagon-like peptide-1 (GLP-1) agonist isolated from the salivary gland venom of:

TEST QUESTIONS

- a. The lizard *Heloderma suspectum* (Gila monster)
b. The rodent-like *Papaver somniferum*
c. The eastern diamondback rattle snake *Crotalus adamanteus*
d. The horseshoe crab *Limulus polyphemus*
- 12.** One of the most common and most serious adverse effects of exenatide in patients receiving sulfonylureas is:
a. Renal toxicity
b. Hepatotoxicity
c. Hypoglycemia
d. Hyperglycemia
- 13.** According to its manufacturer, what is the benefit expected from the availability of the oral formulation of deferasirox?
a. Improved compliance
b. Decreased bone marrow toxicity
c. Increased bioavailability
d. Decreased nephrotoxicity
- 14.** Deferasirox should not be taken with:
a. Ascorbic acid
b. Monoamine oxidase inhibitors
c. Digoxin
d. Aluminum-containing antacids
- 15.** How should deferasirox be taken?
a. Three times a day with food
b. Once a day with food
c. Once daily on an empty stomach
d. Twice daily with water only (no coffee, juice, or any other liquid other than water)
- 16.** Hyaluronidase modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid and is best described as a:
a. Vesicant
b. Spreading or diffusing substance
c. Solubilizing agent
d. Surfactant
- 17.** The Hydase brand of hyaluronidase is produced:
a. From purified bovine testes
b. By recombinant DNA technology
c. From the thyroid glands of beef cattle
d. From the intestinal mucosa of the pig
- 18.** When hyaluronidase is added to a local anesthetic agent, what net effect does this have on the effect of the anesthetic?
a. It delays the onset of the anesthesia.
b. It increases the local vasoconstriction, thereby prolonging the anesthetic effect.
c. It shortens the duration of anesthetic action.
d. It decreases the systemic absorption of the local anesthetic.
- 19.** Mecasermin is indicated for the long-term treatment of growth failure in children with:
a. Severe primary insulin-like growth factor-1 (IGF-1) deficiency
b. Thyroid hormone (TH) gene deletion who have developed neutralizing antibodies to TH
c. Growth failure due to malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids
d. All of the above
- 20.** Caution should be used in combining mecasermin with antidiabetic agents because:
a. The mecasermin antagonizes the hypoglycemic effects of the antidiabetic agent
b. Combined use of these agents increases the risk of developing acute liver necrosis
c. The hypoglycemic effect induced by mecasermin activity may be exacerbated
d. All of the above are likely to occur
- 21.** When should mecasermin be given with respect to meals?
a. Shortly before or after a meal or snack
b. On an empty stomach
c. At bedtime with a large glass of milk
d. At any time without regard to meals
- 22.** Insulin detemir is a long-acting analog of:
a. Glucocorticotropin
b. Determic acid
c. Glucagon-like peptide-1
d. Insulin
- 23.** Which of the following is the most common adverse effect with the use of insulin detemir?
a. Joint pain
b. Renal toxicity
c. Hyperkalemia
d. Hypoglycemia
- 24.** Insulin detemir can be administered by:
a. Intermittent, subcutaneous injection only
b. Subcutaneous injection or constant intravenous infusion
c. Intravenous bolus or subcutaneous injection
d. Intramuscular, subcutaneous, or intravenous injection
- 25.** Micafungin is indicated for:
a. The treatment of esophageal infections caused by *Mycobacterium avium*
b. The prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation
c. The treatment of pulmonary infections with *Histoplasma capsulatum*
d. All of the above
- 26.** In clinical drug-drug interaction studies, which of the following was shown to interact adversely with micafungin?
a. Mycophenolate mofetil
b. Cyclosporine
c. Tacrolimus
d. None of the above
- 27.** The AUC and C_{max} of which of the following drugs were increased by 18% and 42%, respectively, in the presence of steady-state micafungin compared with which drug alone?
a. Ritonivir
b. Nifedipine
c. Substrates of P-glycoprotein
d. All of the above
- 28.** What is the advantage of using a pro-drug NSAID such as nepafenac for topical ophthalmic use compared with traditional ophthalmic NSAIDs?
a. It allows for more rapid penetration to the cornea.
b. It allows for accumulation on the cornea, thus reducing ocular surface complications.
c. It is more stable in solution than the traditional products.
d. All of the above

TEST QUESTIONS

- 29.** Unlike the traditional ophthalmic NSAIDs, nepafenac does not require the removal of contact lenses before administration because it does not contain a preservative.
- True
 - False
- 30.** Nepafenac should not be used in patients concurrently taking:
- Aspirin
 - Monoamine oxidase inhibitors
 - Systemically acting NSAIDs such as ibuprofen
 - None of the above

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ANSWER FORM

NEW DRUG UPDATE 2005—PART 1

FEBRUARY 6 2006 012-999-06-010-H01

Test questions start on page 32.

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