Abstract

Objective: To provide information regarding the most important properties of the new therapeutic agents marketed in the first half of 2010.

Data sources: Product labeling supplemented selectively with published studies and drug information reference sources.

Data synthesis: 13 new therapeutic agents were marketed in the United States during the first half of 2010, 6 of which were reviewed in part 1 of this two-part series. The other seven new drugs marketed during this time period are considered in this article: dienogest/estradiol valerate, sipuleucel-T, romidepsin, collagenase clostridium histolyticum, carglumic acid, ecallantide, and velaglucerase alfa. Indications and information on dosage and administration for these agents are reviewed, as are the most important pharmacokinetic properties, adverse events, drug interactions, and other precautions. Practical considerations for the use of these new agents are also discussed. When possible, the properties of the new drugs are compared with those of older agents marketed for the same indications.

Conclusion: Four of the new drugs considered in this article have mechanisms of action and/or other important properties that distinguish them from previously marketed drugs. Sipuleucel-T is an autologous cellular immunotherapy that has been demonstrated to prolong survival in patients with metastatic castration-resistant prostate cancer. Collagenase clostridium histolyticum is the first drug to be approved for the treatment of Dupuytren’s contracture and provides an alternative to surgery. Ecallantide has a novel mechanism of action (i.e., inhibition of plasma kallikrein), has a broader indication for the treatment of hereditary angioedema, and is administered subcutaneously. Carglumic acid is used for the treatment of acute and chronic hyperammonemia; it has a unique mechanism of action in activating the first enzyme of the urea cycle that converts ammonia into urea. An understanding of the properties of these medications is important for the pharmacist to effectively counsel patients about their use and to serve as a valuable source of information for other health professionals regarding these drugs.

Keywords: New drugs, Food and Drug Administration, drug development, pharmaceutical marketing, risk assessment.

Pharmacy Today. 2010(Nov);16(11):53–63.
Preassessment questions
Before participating in the activity, test your knowledge by answering the following questions. These questions also will be part of the CPE exam.

1. Which of the following drug : use pairings is correct?
   a. Ecallantide : Gaucher disease
   b. Sipuleucel-T: cutaneous T-cell lymphoma (CTCL)
   c. Carglumic acid : hyperammonemia
   d. Velaglucerase alfa : Dupuytren’s contracture

2. Which of the following drug : classification pairings is correct?
   a. Dienogest : estrogen
   b. Romidepsin : histone deacetylase inhibitor
   c. Collagenase clostridium histolyticum : enzyme replacement therapy
   d. Sipuleucel-T : kallikrein inhibitor

3. Which of the following drug : route of administration pairings is correct?
   a. Romidepsin : intramuscular
   b. Carglumic acid : intravenous
   c. Velaglucerase alfa : oral
   d. Ecallantide : subcutaneous

Contraceptive
Dienogest is a new progestin that is used with estradiol valerate in the combination oral contraceptive formulation marketed as Natazia (Bayer). In addition to its gestational action, dienogest also exhibits antiandrogenic activity that is similar to that of drospirenone (the progestin component of Yaz). However, unlike drospirenone, dienogest does not cause hyperkalemia.

Almost all combination oral contraceptive formulations include ethinyl estradiol as the estrogen component. The new product is the first oral contraceptive to use estradiol valerate as the estrogen component, although this agent has been used alone in other formulations for other indications. Estradiol valerate is a prodrug that is converted during absorption and its first pass through the liver to 17-beta estradiol, an endogenous estrogen that is biotransformed to estradiol and subsequently to other metabolites (e.g., estrone).

Dienogest/estradiol valerate is indicated for use by women to prevent pregnancy, although its effectiveness in women with a body mass index greater than 30 kg/m² has not been evaluated. The new product is the first combination oral contraceptive to be used in a four-phase dosage regimen, in which the dosage of the estrogen is decreased and the dosage of the progestin is increased during the cycle in an effort to help avoid breakthrough bleeding. A total of 28 tablets are supplied in a blister pack and should be administered once a day in the following sequence:

- 5 medium-red tablets, each containing 2 mg estradiol valerate and 2 mg dienogest
- 17 light-yellow tablets, each containing 2 mg estradiol valerate and 3 mg dienogest
- 2 dark-red tablets, each containing 1 mg estradiol valerate
- 2 white tablets, inert

As with the other combination hormonal contraceptives, dienogest/estradiol valerate prevents pregnancy primarily by suppressing ovulation. However, other mechanisms that may contribute to its action include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation. In the clinical studies, the new product was highly effective in preventing pregnancy but no data suggest that it is more or less effective than comparable products.

The contraindications and precautions associated with the use of dienogest/estradiol valerate are generally similar to those for the other combination oral contraceptives. A risk of arterial or venous thrombotic events exists, and the new product is contraindicated in patients considered to be at high risk for such complications, including those who have deep-vein thrombosis or pulmonary embolism (currently or in the past), cerebrovascular disease, coronary artery disease, thrombogenic valvular or thrombogenic rhythm diseases of the heart (e.g., atrial fibrillation), inherited or acquired hypercoagulopathies, uncontrolled hypertension, diabetes with vascular disease, headaches with focal neurological symptoms, or migraine headaches if older than 35 years.

Cigarette smoking increases the risk of serious cardiovascular events with the use of combination oral contraceptives. This risk increases with age and the number of cigarettes smoked. The labeling for dienogest/estradiol valerate includes a contraindication and boxed warning that the product should not be used in women who smoke and are older than 35 years.

Dienogest/estradiol valerate is also contraindicated in patients with undiagnosed abnormal genital bleeding, breast cancer or other estrogen- or progestin-sensitive cancer (currently or in the past), or liver tumors or liver disease. The use of the product should be discontinued if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function.

The most commonly reported adverse events in studies of dienogest/estradiol valerate include headache (13%); mottorhagia and irregular menstruation (8%); breast pain, discomfort, or tenderness (7%); nausea or vomiting (7%); acne (4%); and increased weight (3%). Immediate disconnection should be considered in women who experience an increase in frequency or severity of migraine headaches. Breakthrough bleeding and spotting sometimes occur, particularly during the first 3 months of use. Chloasma has been experienced by some women using oral contraceptives, and those with a predisposition to this response should avoid exposure to the sun or ultraviolet radiation while taking dienogest/estradiol valerate.

Oral contraceptives may cause an increase in blood pressure and decrease glucose tolerance. The use of dienogest/estradiol valerate is contraindicated in women with uncontrolled
hypertension and/or diabetes with vascular disease. Blood pressure should be monitored in women with well-controlled hypertension, and diabetic and prediabetic women should be closely monitored.

Dienogest/estradiol valerate is classified in Pregnancy Category X and is contraindicated in women who are pregnant. The use of an oral contraceptive should be discontinued if pregnancy is confirmed. Pregnancy should be ruled out in the event of amenorrhea occurring in two or more consecutive cycles. Because estrogens can reduce milk production in breast-feeding mothers, nursing mothers should be advised to use other forms of contraception until the child is weaned.

Estradiol valerate is extensively metabolized (primarily via cytochrome P450 [CYP3A pathways] in the gastrointestinal mucosa and via extensive first-pass metabolism. Approximately 95% of a dose is metabolized before entering the systemic circulation. The bioavailability of dienogest is approximately 90% and it is extensively metabolized via the CYP3A4 pathway.

The concurrent use of drugs or herbal remedies that cause enzyme induction may reduce the effectiveness of oral contraceptives or increase breakthrough bleeding. Women who are using strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John’s wort) should not use dienogest/estradiol valerate as their contraceptive while using these inducers and for at least 28 days following discontinuation of the inducer. Women who are using a moderate or weak enzyme inducer (e.g., barbiturates, topiramate) should be advised to use an alternative method of contraception or a backup method to the oral contraceptive.

The use of a CYP3A4 inhibitor (e.g., ketoconazole, erythromycin, ritonavir, verapamil, grapefruit juice) with dienogest/estradiol valerate should be anticipated to increase concentrations of lamotrigine (e.g., Lamictal), probably via induction of its glucuronidation. Therefore, increasing the dosage of this antiepileptic drug may be necessary if dienogest/estradiol valerate is used concurrently.

The use of dienogest/estradiol valerate should be started on day 1 of the menstrual cycle (i.e., the first day of menstrual bleeding). One tablet should be taken at the same time every day in the order directed on the package. A nonhormonal contraceptive should be used as backup during the first 9 days of use of the new product. If severe vomiting or diarrhea is experienced, absorption may not be complete and additional contraceptive measures should be used. If vomiting or diarrhea occurs within 4 hours after taking a colored tablet, it should be considered a missed tablet.

Tablets should not be skipped, and administration should not be delayed by more than 12 hours. The labeling for the product should be consulted for instructions if one or more doses are missed or when women are switching from use of another hormonal contraceptive to dienogest/estradiol valerate. For postpartum women who do not breastfeed or after a second trimester abortion, dienogest/estradiol valerate should be started no earlier than 4 weeks postpartum.

If major surgery or other surgeries known to have an increased risk of thromboembolism are anticipated, discontinuing combination oral contraceptives at least 4 weeks before and through 2 weeks after surgery is advised.

Antineoplastic agents

Sipuleucel-T

Prostate cancer is the second most common type of cancer in men in the United States, following skin cancer. In 2009, almost 200,000 new cases of prostate cancer were diagnosed. The treatment of prostate cancer may include surgery, radiation, and/or medications (e.g., androgen deprivation therapy). Although hormonal treatment has been effective in many men, metastatic disease may often become resistant to this therapy, and a regimen based on docetaxel (e.g., Taxotere) has been the

www.pharmacist.com NOVEMBER 2010 • PHARMACY TODAY 55
only treatment that has been demonstrated to prolong survival in men with hormone refractory prostate cancer.

Sipuleucel-T (Provenge—Dendreon) is an autologous cellular immunotherapy that is also designated as a therapeutic vaccine. The preparation of the product initially requires the collection of a patient’s peripheral blood mononuclear cells using a leukapheresis procedure approximately 3 days before the infusion date. The product contains these cells, including antigen-presenting cells (APCs), that have been activated in a culture medium with a recombinant human protein. PAP-GM-CSF, that consists of prostatic acid phosphatase (PAP; an antigen expressed in most prostate cancers) linked to granulocyte-macrophage colony-stimulating factor (GM-CSF; an immune cell activator). The active components of sipuleucel-T are autologous APCs and PAP-GM-CSF. During culture, the APCs can bind with and process the recombinant antigen into small peptides that are then displayed on the surface of the APCs. Although the mechanism of action is not completely understood, the product is designed to induce an immune response targeted against PAP.

Sipuleucel-T is administered by intravenous infusion and is indicated for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant (hormone-refractory) prostate cancer. Its effectiveness was demonstrated in placebo-controlled studies in which those in the control group also underwent leukapheresis procedures but received autologous peripheral blood mononuclear cells that had not been activated. Although the times to disease progression for the two groups did not differ enough to be considered statistically significant, the median survival was significantly longer in the group of patients receiving sipuleucel-T (25.8 months vs. 21.7 months in the largest study).

The most important risk experienced with the use of sipuleucel-T is acute infusion reactions consisting of responses such as fever, chills, dyspnea, nausea, fatigue, hypertension, and/or tachycardia. Most of these events were mild to moderate in severity, but in the controlled studies, approximately 4% of patients experienced severe (grade 3) reactions. To reduce the potential for acute infusion reactions, patients should be premedicated orally with acetaminophen and an antihistamine such as diphenhydramine approximately 30 minutes before administration of the drug.

The most frequently reported adverse events included chills (53%), fatigue (41%), fever (31%), back pain (30%), nausea (22%), joint ache (20%), and headache (18%). Treatment with sipuleucel-T was discontinued in 2% of patients as a result of adverse events.

Because sipuleucel-T is designed to stimulate the immune system, the concurrent use of an immunosuppressive agent (e.g., systemic corticosteroids) or chemotherapy may reduce the effectiveness of the new drug. The concomitant use of these agents has not been studied, but patients already being treated with an immunosuppressive agent should be evaluated to determine whether it is appropriate to discontinue or reduce the dosage of this medication before treatment with sipuleucel-T.

The recommended course of treatment with sipuleucel-T is three doses, administered at approximately 2-week intervals. Approximately 3 days before each dose, the patient’s immune cells are collected using a leukapheresis procedure. The cells are sent to a center at which they are mixed with PAP-GM-CSF. The product is supplied in an infusion bag in a special insulated polyurethane container that is placed in a cardboard shipping box and sent to the provider for infusion administration. The infusion bag should remain in the insulated container until the time of administration.

Each dose of sipuleucel-T contains a minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF in Lactated Ringer’s Injection. The product is supplied as a suspension in an infusion bag containing a volume of 250 mL. The medication is for autologous use only, and before infusion, the patient’s identity must be matched with the patient identifiers on the infusion bag and the pertinent form provided with the product.

Sipuleucel-T is administered via intravenous infusion over a period of approximately 60 minutes until the entire volume has been infused. A cell filter should not be used. Although premedication may reduce the occurrence and severity of infusion reactions, patients should be observed for at least 30 minutes following each infusion. If an acute infusion reaction occurs, the infusion may be interrupted or slowed, depending on the severity of the reaction. In clinical studies, acute infusion reactions were treated with acetaminophen, intravenous antihistamines, and low doses of intravenous meperidine.

Sipuleucel-T is not routinely tested for transmissible infectious diseases. Therefore, the drug and patient leukapheresis material may carry the risk of transmitting infectious diseases to individuals handling the product. Universal precautions should be used by those with responsibilities that may place them at risk.

The cost of sipuleucel-T is approximately $93,000 for the three-dose course of treatment. The cost of the treatment has fueled the debate as to whether individuals and society can afford the use of such expensive therapies for which the benefit is of brief duration. The availability of the drug also raises the questions of whether it will be used off label (e.g., for earlier-stage prostate cancer) and whether health insurance programs will cover such use.

Another new drug for the treatment of prostate cancer was marketed in the second half of 2010. Cabazitaxel (Jevtana—Sanofi-Aventis) is indicated for use in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen. This drug will be considered in a subsequent article.

Romidepsin
Cutaneous T-cell lymphoma (CTCL) is a general term for a group of non-Hodgkin lymphomas in which malignant T cells typically manifest initially in the skin. Approximately 20,000 patients in the United States have been diagnosed with this disorder, the most common forms of which are mycosis fungoides and a more aggressive variant known as Sezary syndrome.

www.pharmacytoday.org
Skin lesions associated with CTCL are often pruritic, sometimes intensely so, and can be painful. The lesions may become ulcerative and necrotic, and patients with later-stage CTCL are highly susceptible to infection because their skin barrier is compromised. Although CTCL initially involves the skin, systemic involvement of the lymph nodes, spleen, liver, or other viscera can occur with time.

In the early stages of CTCL, symptoms may often be effectively managed with topical corticosteroids and other “skin-directed” therapies. In more advanced stages of the disease, systemic therapies such as the oral retinoid bexarotene (Targretin) and denileukin diftitox (Ontak) have been used. In 2006, vorinostat (Zolinza) was marketed for the treatment of cutaneous manifestations in patients with CTCL who have progressive, persistent, or recurrent disease on or following two systemic therapies. Vorinostat was the first antineoplastic agent that worked by inhibiting the activity of histone deacetylases (HDACs), enzymes that catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. In some cancer cells, an overexpression of HDACs occurs, and the inhibition of HDAC activity by vorinostat provides a beneficial response in some patients with CTCL.

Romidepsin (Istodax—Gloucester) is the second HDAC inhibitor to be approved for the treatment of patients with CTCL. Unlike vorinostat, which is administered orally, romidepsin is administered via intravenous infusion and is specifically indicated for the treatment of CTCL in patients who have received at least one previous systemic therapy. The effectiveness of romidepsin was demonstrated in two clinical studies in patients who had received prior therapies. The overall response (i.e., a reduction in tumor size) rate was 35%, and 6% of patients experienced a complete response. The median duration of response was 15 months in one study and 11 months in the other. The new drug has not been directly compared with vorinostat in clinical studies.

The frequency with which adverse events were reported differed substantially in the two studies of romidepsin. The serious adverse events reported most frequently (incidences noted for all patients and for patients having an adverse event of grade 3 or 4 severity, respectively) in the patients in study 1 included infection (46% and 11%), sepsis, and pyrexia (20% and 4%), whereas the serious adverse events reported most often in study 2 were nausea (36% and 6%), infection (54% and 33%, including six deaths), central line infection, fatigue (77% and 14%), thrombocytopenia (65% and 14%), neutropenia (57% and 27%), leukopenia (46% and 22%), edema, supraventricular dysrhythmia, and ventricular dysrhythmia.

Other adverse events frequently experienced (incidences for all patients) by the patients in study 1 included nausea (56%), fatigue (53%), vomiting (34%), and anorexia (23%), whereas the patients in study 2 commonly experienced anemia (72%), electrocardiogram ST-T wave changes (63%), and lymphopenia (57%).

Because romidepsin may cause electrocardiographic changes, appropriate cardiovascular monitoring precautions (e.g., monitoring of potassium and magnesium concentrations) should be observed, particularly in patients with congenital long QT syndrome, with considerable cardiovascular disease, and who are taking antisyndrhythmic agents and/or other medications that may cause substantial QT prolongation. Hematological parameters should also be monitored, as the occurrence of thrombocytopenia, neutropenia, lymphopenia, and/or anemia may necessitate a reduction in dosage or interruption in therapy.

Romidepsin may cause harm to the fetus if administered during pregnancy, and it is classified in Pregnancy Category D. Although whether the drug is excreted in human milk is not known, a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of romidepsin in pediatric patients have not been established.

Romidepsin undergoes extensive metabolism, primarily via the CYP3A4 pathway. Although it has not been specifically studied in patients with hepatic or renal impairment, caution should be exercised when it is used in patients with moderate and severe hepatic impairment or with end-stage renal disease.

The potential for romidepsin to interact with other medications has not been specifically studied. However, prolongation of prothrombin time and increased international normalized ratio (INR) have been reported in a patient treated with the new drug who was also taking warfarin. Accordingly, such concurrent therapy should be carefully monitored. Romidepsin binds to estrogen receptors and may reduce the effectiveness of estrogen-containing contraceptives. Alternative or additional contraceptive measures should be used in women of childbearing potential who are to be treated with the new drug.

Romidepsin is a substrate for CYP3A4 and for P-glycoprotein. Its action may be increased by the concurrent use of a strong CYP3A4 inhibitor (e.g., clarithromycin) or decreased by the concurrent use of a potent CYP3A4 inducer (e.g., carbamazepine, rifampin, St. John's wort). The concurrent use of such inhibitors or inducers with romidepsin should be avoided if possible.

The recommended dosage of romidepsin is 14 mg/m² administered by intravenous infusion over a 4-hour period on days 1, 8, and 15 of a 28-day cycle. Cycles of treatment are repeated every 28 days provided that the patient continues to benefit from and tolerates the therapy. The product labeling should be consulted for the treatment and dosage recommendations in patients who experience hematologic or nonhematologic toxicities.

Romidepsin is supplied as a kit that includes a single-use vial containing a lyophilized powder with 10 mg of the drug and 20 mg of the bulking agent, povidone. The kit also includes a vial containing 2 mL of the diluent consisting of 80% propylene glycol and 20% dehydrated alcohol. The medication must be reconstituted with the diluent supplied and then diluted in 500 mL of 0.9% Sodium Chloride Injection. The solution should be administered as soon after dilution as possible. However, it is stable for at least 24 hours at room temperature.
Agent for Dupuytren’s contracture

Dupuytren’s contracture is a connective tissue disease in which collagen is deposited beneath the skin in the palm of the hand. When too much collagen builds up, thick, rope-like cords of tissue are formed that extend to the base of the fingers and may reduce the ability to straighten and use the fingers in the normal manner. This potentially debilitating condition is most common in white men older than 50 years, and until recently, the only effective treatment was surgery.

Collagenase clostridium histolyticum (Xiaflex—Auxilium) consists of two microbial collagenases, collagenase AUX-1 and collagenase AUX-2, obtained from the fermentation of Clostridium histolyticum bacteria. Each enzyme consists of approximately 1,000 amino acids, and the two enzymes are thought to act synergistically in hydrolyzing collagen with a resultant lysis of collagen deposits. The new product is specifically indicated for intralesional use in the treatment of adult patients with Dupuytren’s contracture with a palpable cord.

The effectiveness of collagenase clostridium histolyticum was demonstrated in two studies in which the primary endpoint was a reduction in contracture of the selected primary joint (metacarpophalangeal [MP] joint or proximal interphalangeal [PIP] joint). Treatment was successful in 64% and 44% of the patients treated with the new drug and 7% and 5% of the patients receiving placebo, respectively. Patients treated with the medication also showed a greater increase from baseline in the range of motion of the joints compared with those receiving placebo. The surgical treatment of Dupuytren’s contracture is usually associated with a long recovery and a need for physical therapy, and the availability of collagenase clostridium histolyticum represents an important advance in the treatment of this condition. In addition, the recurrence rate with the new drug (4%) is considerably lower than that following surgery.

The use of collagenase clostridium histolyticum is also being studied in patients with Peyronie’s disease and frozen shoulder syndrome. However, these are not labeled indications at the present time.

The most important concern with the use of collagenase clostridium histolyticum is the risk of tendon rupture or other serious injury to the injected extremity. The drug should be injected only into the collagen cord with a MP or PIP joint contracture, and caution should be exercised in avoiding injection into tendons, nerves, blood vessels, or other collagen-containing structures of the hand, as permanent injury may result.

Although none of the patients in the clinical studies experienced a severe allergic reaction with the use of collagenase clostridium histolyticum, a potential for such a response should be recognized. Mild allergic reactions (pruritus) were reported in 15% of the patients treated with the new drug, compared with 1% of those receiving placebo.

In the clinical studies, 70% and 38% of patients experienced contusion/ecchymosis and injection-site hemorrhage, respectively, following the injection of collagenase clostridium histolyticum. The safety of concurrent use of medications having anticoagulant activity is not known (other than low-dose aspirin up to 150 mg/day), and caution must be exercised in patients being treated with medications such as warfarin, clopidogrel (Plavix), or prasugrel (Effient).

Other commonly reported adverse events with collagenase clostridium histolyticum include peripheral edema (i.e., of the injected hand; 73%), injection-site reaction (e.g., erythema, irritation; 35%), and pain in extremity (35%). Neutralizing antibodies to the new collagenase enzymes were detected in approximately 20% of patients. However, no apparent correlation existed between antibody frequency, antibody titer, or neutralizing status and clinical response or adverse events.

Collagenase clostridium histolyticum is classified in Pregnancy Category B. Its effectiveness and safety in patients younger than 18 years have not been established.

Collagenase clostridium histolyticum is supplied as a lyophilized powder in single-use vials containing 0.9 mg of the drug. The vials should be stored in a refrigerator. The drug should be reconstituted with 0.39 mL (for a MP joint) or 0.31 mL (for a PIP joint) of the sterile diluent supplied with the medication (0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride) before intralesional injection into a Dupuytren’s cord. The calcium included in the diluent is required for the activity of the drug. The drug should be administered by a health care provider who is experienced in injection procedures of the hand and in the treatment of patients with Dupuytren’s contracture. The product labeling should be consulted for the detailed guidelines for reconstitution of the medication, preparation before injection, and injection procedure.

The recommended dose of collagenase clostridium histolyticum is 0.58 mg per injection into a palpable cord (i.e., 0.25 mL reconstituted solution in cords affecting MP joints, 0.20 mL for cords affecting PIP joints). After confirming that the injection needle is correctly placed in the cord, approximately one-third of the dose should be injected. The needle tip should then be withdrawn and repositioned in a slightly more distal location, and another one-third of the dose should be injected. The needle tip is then withdrawn and repositioned again to inject the final portion of the dose. The patient should keep the injected hand elevated until bedtime and return to the provider’s office the next day. If a contracture remains when the patient is evaluated the following day, a passive finger extension procedure should be performed to facilitate cord disruption. If the first finger extension procedure does not result in disruption of the cord, a second and third attempt can be performed at 5- to 10-minute intervals.

If the cord has not been disrupted after three attempts, a follow-up visit may be scheduled in approximately 4 weeks. If the contracted cord persists to the time of the subsequent visit, an additional injection with finger extension procedures may be performed.

Following finger extension procedures, patients should be fitted with a splint and provided instructions for use at bedtime for up to 4 months to maintain finger extension. The patient should also perform finger extension and flexion exercises several times a day for several months.
Agent for hyperammonemia

Carbamoyl phosphate synthetase (CPS)-1 is the first enzyme of the urea cycle, which converts ammonia into urea. This enzyme is activated by N-acetylglutamate (NAG), which is the product of the hepatic enzyme NAG synthase (NAGS). Some individuals experience a rare genetic disorder that is caused by a deficiency of NAGS and that may be evident soon after birth. This enzyme deficiency can result in a rapid increase in ammonia concentrations, which can be a life-threatening emergency. If not recognized and treated quickly, acute symptomatic hyperammonemia may cause neurologic complications and potentially fatal brain injury/damage.

**Carglumic acid** (Carbaglu—Orphan Europe) is a synthetic analog of NAG that acts as a replacement for NAG and activates CPS-1 in patients with NAGS deficiency. The new drug has been approved for use in pediatric and adult patients as adjunctive therapy for the treatment of acute hyperammonemia and for maintenance therapy of chronic hyperammonemia, which is caused by the deficiency of the hepatic enzyme NAGS. In treating patients with acute hyperammonemia, other ammonia-lowering therapies (i.e., sodium phenylbutyrate [Buphenyl], sodium benzoate/sodium phenylacetate [Ucephan, Ammonul]) and hemodialysis should be used concurrently with carglumic acid. Protein restriction and hypercaloric intake also are recommended to block ammonia-generating catabolic pathways. During maintenance treatment, the concomitant use of other ammonia-lowering therapies may be reduced or discontinued based on plasma ammonia concentrations. When these concentrations have normalized, protein intake usually can be increased, and the goal is to permit unrestricted protein intake.

The effectiveness of carglumic acid has been evaluated in a retrospective review of the clinical course of 23 patients with NAGS deficiency who were treated with the new drug for a median of approximately 8 years. Plasma ammonia concentrations were reduced within 24 hours following initiation of treatment, with or without the concomitant use of other ammonia-lowering therapies. By the third day of treatment, normal plasma ammonia concentrations were attained for all patients with available data.

The adverse events most often experienced with the use of carglumic acid included vomiting (26%), abdominal pain (17%), pyrexia (17%), tonsillitis (17%), anemia (13%), ear infection (13%), nasopharyngitis (13%), headache (13%), and diarrhea (13%). The new agent is classified in Pregnancy Category C. All of the patients who were evaluated in the retrospective review of the clinical course of carglumic acid treatment began treatment during infancy or childhood.

The recommended initial dosage of carglumic acid for the treatment of acute hyperammonemia is 100 to 250 mg/kg/day. The total daily dosage should be divided into two to four doses that, in the treatment of adult patients, should be rounded to the nearest 100 mg (one-half tablet). Plasma ammonia concentrations should be regularly monitored, and the maintenance dosage should be titrated based on the response to treatment. Maintenance dosages are usually less than 100 mg/kg/day.

Carglumic acid scored tablets are supplied in a 200-mg potency. The tablets should not be swallowed whole or crushed. For use in adult patients, each tablet should be dispersed in a minimum of 2.5 mL water and taken immediately. Because the tablets do not completely dissolve in water and undissolved particles of the tablet may remain in the mixing container, the container should be rinsed with an additional volume of water and the contents swallowed immediately. The mixing of carglumic acid in other liquids or foods has not been evaluated and is not recommended.

In pediatric patients, doses of carglumic acid are administered using an oral syringe. Each tablet is mixed in a container with 2.5 mL water to provide a concentration of 80 mg/mL. The mixture is shaken gently to disperse the medication. The appropriate volume of the dispersion is drawn up in an oral syringe and administered immediately. The unused portion should be discarded. The oral syringe should be refilled with a minimum volume of water (1–2 mL) and administered immediately. Carglumic acid also may be administered via a nasogastric tube in both adult and pediatric patients.

Agent for hereditary angioedema

Hereditary angioedema (HAE) is a rare genetic disorder that affects approximately 10,000 people in the United States. It is characterized by severe and often painful swelling that most often occurs in the extremities, face, gastrointestinal tract, and/or larynx. Asphyxiation/death may occur as a consequence of the swelling of the larynx. HAE attacks are recurrent and usually unpredictable, and patients, on average, experience more than 20 attacks per year.

HAE is caused by a mutation of the C1-INH gene that results in a deficiency of C1 esterase inhibitor (C1-INH). C1-INH regulates inflammatory and clotting reactions, primarily by acting as an inhibitor of plasma kallikrein. The kallikrein–kinin system is a complex proteolytic cascade, and unregulated activity of plasma kallikrein results in the excessive production of bradykinin, a vasodilator that is thought to be responsible for the symptoms that are characteristic of HAE.

Certain androgens such as danazol, which increases hepatic production of C1-INH, have been used for HAE prophylaxis. However, these agents are of limited effectiveness in many patients and have been associated with the occurrence of serious adverse events. In 2008, C1-INH (human; Cinryze) derived from human plasma was marketed for intravenous use for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE. Subsequently, another C1-INH product (Berinert) was marketed for intravenous use for the treatment of acute abdominal or facial attacks of HAE in adults and adolescents.

**Ecallantide** (Kalbitor—Dyax) is a 60–amino acid protein produced in yeast cells by recombinant DNA technology. It is a selective, reversible inhibitor of plasma kallikrein that is administered subcutaneously and indicated for the treatment of acute attacks of HAE in patients 16 years or older. By inhibiting kallikrein, ecallantide reduces the formation of bradykinin,
thereby reducing the symptoms of an acute episodic attack of HAE. It is the second agent to be approved for the treatment of acute HAE attacks, joining the Berinert formulation of C1-INH, but the labeled indication for ecallantide is not limited to the treatment of abdominal and facial attacks.

The effectiveness of ecallantide was evaluated in two placebo-controlled studies in which the severity of symptoms and treatment outcome were assessed at baseline, 4 hours, and 24 hours. In both studies, patients treated with ecallantide experienced greater reduction in symptoms and improved outcomes compared with those receiving placebo. More patients in the placebo group (50%) required medical intervention to treat unresolved symptoms within 24 hours compared with the ecallantide-treated group (33%). Ecallantide and C1-INH have not been directly compared in clinical studies.

The most important concern with the use of ecallantide is the risk of hypersensitivity reactions, including anaphylaxis, which is the subject of a boxed warning in the labeling for the new drug. Anaphylaxis was experienced by 4% of the patients in the clinical studies, and the reactions occurred within the first hour after administration. The symptoms of a hypersensitivity reaction and the symptoms of HAE are similar, and patients should be monitored closely for an appropriate period of time following administration of the drug. The use of ecallantide is contraindicated in patients who have experienced a hypersensitivity reaction with its previous use.

The most commonly reported adverse events with ecallantide included headache (16%), nausea (13%), fatigue (12%), diarrhea (11%), upper respiratory tract infection (8%), injection-site reactions (7%), nasopharyngitis (6%), vomiting (6%), pruritus (5%), upper abdominal pain (5%), and pyrexia (5%). When administered intravenously rather than subcutaneously as recommended, ecallantide has been reported to prolong activated partial thromboplastin time—a result that is likely related to its effect on the intrinsic coagulation pathway. Approximately 7% of patients seroconverted to anti-ecallantide antibodies. These individuals may be at a higher risk of a hypersensitivity reaction.

Ecallantide is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus. Its effectiveness and safety in patients younger than 16 years have not been evaluated.

Ecallantide is supplied in vials containing 10 mg of the drug in 1 mL solution. The vials should be stored in a refrigerator. The drug is administered subcutaneously in the abdomen, thigh, or upper arm. The recommended dose is 30 mg administered in three injections containing 10 mg each (i.e., using three vials). A 10-mg dose of the drug (1 mL) should be withdrawn from the vial using a large-bore needle. The needle on the syringe should then be changed to a needle suitable for subcutaneous injection (27 gauge). This procedure should be repeated for each of the three vials used to provide the total dose of 30 mg. The injection site for each of the three injections may be in the same or different anatomic locations. Injection sites should be separated by at least 5 cm (2 in) and away from the anatomical site of the HAE attack. If the HAE attack persists following the initial 30-mg dose, an additional dose of 30 mg may be administered within a 24-hour period.

**Agent for Gaucher disease**

Gaucher disease is a rare autosomal recessive lysosome storage disorder caused by mutations in the GBA (glucosidase beta acid) gene. These mutations result in a deficiency of beta-glucocerebrosidase, which is a lysosomal enzyme that catalyzes the conversion of the sphingolipid glucocerebroside into glucose and ceramide. The deficiency of beta-glucocerebrosidase results in an accumulation of glucocerebroside in the lysosomal compartment of macrophages. These “Gaucher cells” primarily accumulate in the liver, spleen, and bone marrow, as well as in other organs, leading to complications such as anemia, thrombocytopenia, and organomegaly.

Fewer than 1 in 100,000 people in the general population in the United States have a mutation for Gaucher disease. However, it is more common among Jewish people of eastern European (Ashkenazi) ancestry. Type 1 Gaucher disease is the most common form, and anemia, thrombocytopenia, and organomegaly are the most common manifestations. Type 2 disease is also characterized by brain damage and early death, and patients with type 3 disease also experience brain involvement such as seizures.

Imiglucerase (Cerezyme) is a glycoprotein of 497 amino acids that has been the standard of treatment for type 1 Gaucher disease since it was first marketed in 1994. It is an analog of beta-glucocerebrosidase produced using recombinant DNA technology that differs from the human enzyme only at one position where histidine is substituted for arginine. A recent shortage of imiglucerase has created a need to identify effective alternatives for treatment. Although the glucosylceramide synthase inhibitor miglustat (Zavesca) is used in the treatment of Gaucher disease, it is indicated only for adult patients with mild to moderate type 1 disease for whom enzyme replacement therapy (ERT) is not a therapeutic option.

*Velaglucerase alfa* (Vpriv—Shire) has the same amino acid sequence as the human enzyme glucocerebrosidase and is produced by gene activation technology in a human fibroblast cell line. Its action as a hydrolytic lysosomal glucocerebrosidase-specific enzyme is essentially the same as that of imiglucerase, and it is indicated for intravenous administration for long-term ERT for pediatric and adult patients with type 1 Gaucher disease. The effectiveness of velaglucerase alfa was demonstrated in two studies in patients who were not currently receiving Gaucher disease–specific therapy. There was a clinically meaningful increase in hemoglobin concentration, which was the primary endpoint, and an increase in platelet count, as well as a reduction in liver volume and spleen volume. A third study was conducted in patients who were receiving a biweekly dose of imiglucerase for at least the 6-month period immediately before changing treatment to velaglucerase alfa. Hemoglobin concentrations and platelet counts remained stable on average through 12 months of treatment with the new drug.

Hypersensitivity reactions have occurred in some patients treated with velaglucerase alfa, and caution should be exert-
cised when considering its use in patients who have experienced symptoms of hypersensitivity to the new drug or to other ERIs. Infusion-related reactions were the most commonly reported adverse events (52%) in patients who had not previously received imiglucerase and included headache (35%), dizziness (22%), pyrexia (22%), asthenia/fatigue (13%), hypotension (<10%), and hypertension (<10%). These reactions were usually mild and occurred most often during the first 6 months of treatment and less frequently thereafter. Patients were not routinely provided with premedications before infusion of the drug in the clinical studies; however, pretreatment with an antihistamine and/or corticosteroid may prevent subsequent reactions in patients for whom treatment of symptoms of infusion reactions was required.

Other adverse events reported with the use of velaglucerase alfa in the clinical studies included upper respiratory tract infection (32%), abdominal pain (19%), back pain (17%), joint pain (knee; 15%), and prolongation of activated partial thromboplastin time (aPTT; 11%). Upper respiratory tract infections, rash, pyrexia, and prolonged aPTT were more commonly experienced in pediatric patients than in adults.

As with other therapeutic proteins, a potential for immunogenicity exists with the use of velaglucerase alfa. In the clinical studies, only 1 of the 54 patients who had not been previously treated with imiglucerase developed immunoglobulin G class antibodies to velaglucerase alfa. The labeling for imiglucerase notes that 15% of patients receiving it experience the formation of antibodies. However, whether the difference suggested in the limited data for the two drugs is associated with a clinically important reduction in the potential for immunogenicity for velaglucerase alfa is not known.

Velaglucerase alfa is classified in Pregnancy Category B. Whether it is excreted in human milk is unknown, and caution should be exercised if administered to a nursing woman. The effectiveness and safety of the new drug have been established in pediatric patients as young as 4 years of age.

The recommended dosage of velaglucerase alfa is 60 units/kg every other week administered as a 60-minute infusion. The usual dosage and frequency of administration are the same as for imiglucerase. Patients who are being treated with a stable dose of imiglucerase who are to be switched to the new drug should be treated with the same dosage of velaglucerase alfa. Dosages of velaglucerase alfa ranging from 15 to 60 units/kg have been evaluated in clinical studies. Velaglucerase alfa should be administered under the supervision of a health professional.

Velaglucerase alfa is supplied as a lyophilized powder in single-use vials containing 200 and 400 units per vial. The vials should be stored in a refrigerator. Following determination of the number of vials needed to provide the calculated dose, the contents of each vial should be reconstituted with 2.2 or 4.3 mL Sterile Water for Injection for the 200- and 400-unit vials, respectively. The resultant solution contains 100 units of the drug in each milliliter. The calculated volume of the solution needed to provide the dose should be withdrawn from the appropriate number of vials and diluted in 100 mL of 0.9% sodium chloride solution suitable for intravenous administration. In both the reconstitution and dilution steps, the contents should be mixed gently and must not be shaken.

The diluted solution should be administered over 60 minutes and should not be infused with other products in the same infusion tubing. The solution should be filtered through an in-line low protein–binding 0.2-µm filter during administration. The solution of velaglucerase alfa should be administered immediately following preparation. If this is not possible, the solution may be stored in a refrigerator for up to 24 hours.

The cost of imiglucerase treatment is approximately $200,000 a year, and the cost of velaglucerase alfa is approximately 15% less than this amount.
CPE exam

Instructions: The assessment test for this activity must be taken online; please see “CPE processing” below for further instructions. There is only one correct answer to each question. This CPE activity will be available at www.pharmacist.com no later than November 30, 2010.

1. Which of the following drug : use pairings is correct?
   a. Ecallantide : Gaucher disease
   b. Sipuleucel-T : cutaneous T-cell lymphoma (CTCL)
   c. Carglumic acid : hyperammonemia
   d. Velaglucerase alfa : Dupuytren contracture

2. Which of the following drug : classification pairings is correct?
   a. Dienogest : estrogen
   b. Romidepsin : histone deacetylase inhibitor
   c. Collagenase clostridium histolyticum : enzyme replacement therapy
   d. Sipuleucel-T : kallikrein inhibitor

3. Which of the following drug : route of administration pairings is correct?
   a. Romidepsin : intramuscular
   b. Carglumic acid : intravenous
   c. Velaglucerase alfa : oral
   d. Ecallantide : subcutaneous

4. Which of the following agents has a boxed warning in its labeling regarding the risk of anaphylaxis?
   a. Ecallantide
   b. Romidepsin
   c. Collagenase clostridium histolyticum
   d. Velaglucerase alfa

5. With the use of which of the following agents is the use of acetaminophen and an antihistamine as premedications recommended?
   a. Carglumic acid
   b. Romidepsin
   c. Ecallantide
   d. Sipuleucel-T

6. Which of the following agents is most likely to cause thrombocytopenia as an adverse event?
   a. Velaglucerase alfa
   b. Romidepsin
   c. Carglumic acid
   d. Dienogest

7. Which of the following agents is designated as a therapeutic vaccine?
   a. Velaglucerase alfa
   b. Collagenase clostridium histolyticum
   c. Sipuleucel-T
   d. Ecallantide

8. Which of the following statements is correct regarding dienogest?
   a. It exhibits androgenic activity.
   b. Its activity is most similar to that of drospirenone.
   c. Hyperkalemia is a common adverse event associated with its use.
   d. It is available for use as a single agent and in combination formulations with an estrogen.

9. Which of the following statements is correct regarding estradiol valerate?
   a. It is a prodrug that is converted to ethinyl estradiol.
   b. It is used in combination with dienogest as a contraceptive product that is used in a triphasic dosage regimen.
   c. Its use is contraindicated in women who smoke.
   d. A nonhormonal contraceptive should be used as backup during the first 9 days of its use as a contraceptive.

10. Which of the following statements is correct regarding sipuleucel-T?
   a. It induces an immune response that is targeted against prostate-specific acid phosphatase.
   b. It is indicated for the initial treatment of prostate cancer to reduce the possibility of metastasis.
   c. It should be used in combination with an immunosuppressant such as cyclosporine.
   d. Bone marrow suppression is the most important risk associated with its use.

11. Which of the following statements is correct regarding sipuleucel-T?
   a. Its preparation includes use of a patient’s own blood cells.
   b. It is used as part of a regimen that also includes erythropoietin.
   c. It is administered as a bolus intravenous injection.
   d. It is administered every 6 months for a total of three doses.

12. Which of the following statements is correct regarding romidepsin?
   a. Its properties are most similar to those of bexarotene.
   b. It is indicated for the initial treatment of CTCL.
   c. It should be used as part of a regimen that also includes vorinostat.
   d. Infection is one of the important risks associated with its use.
13. Which of the following statements is correct regarding romidepsin?
   a. It is excreted unchanged in the urine.
   b. Its action may be reduced by the concurrent use of clarithromycin.
   c. It binds to estrogen receptors and may reduce the effectiveness of estrogen-containing contraceptives.
   d. It is administered once every 28 days.

14. Which of the following statements is correct regarding collagenase clostridium histolyticum?
   a. It is injected into fingers in which excessive amounts of collagen have been deposited.
   b. It consists of two enzymes that are thought to act synergistically in hydrolyzing collagen.
   c. It should be used in conjunction with an anticoagulant to reduce the risk of clot formation.
   d. An antihistamine should be administered before treatment to reduce the possibility of an allergic response.

15. Which of the following statements is correct regarding collagenase clostridium histolyticum?
   a. Recurrence of collagen deposits is more likely to occur with its use than following surgery.
   b. A rash at the injection site is the most common adverse event associated with its use.
   c. A dose is divided into three separate injections.
   d. It is administered once a month for up to four doses.

16. Which of the following statements is correct regarding carglumic acid?
   a. It is a synthetic analog of N-acetylglutamate.
   b. It inhibits carbamoyl phosphate synthetase 1.
   c. It reduces the conversion of urea to ammonia.
   d. It is used in conjunction with protein supplementation.

17. Which of the following statements is correct regarding carglumic acid?
   a. It has a slow onset of action, and normal ammonia concentrations are not attained until at least 10 days after initiating treatment.
   b. Its effectiveness has not been established in patients younger than 18 years.
   c. It is administered two to four times a day.
   d. It is administered orally or intravenously.

18. Which of the following statements is correct regarding ecallantide?
   a. It increases the production of C1 esterase inhibitor (C1-INH) in the liver.
   b. It replaces C1-INH in patients with a genetic deficiency.
   c. It has been approved for the prevention and treatment of hereditary angioedema.
   d. Its use results in the reduction of the formation of bradykinin.

19. Which of the following statements is correct regarding ecallantide?
   a. It is extensively metabolized via the cytochrome P450 3A4 metabolic pathway.
   b. The recommended dose is administered as three separate injections.
   c. It is administered intravenously.
   d. It is administered every 24 hours for up to seven doses.

20. Which of the following statements is correct regarding velaglucerase alfa?
   a. Infusion-related reactions are the most common adverse event associated with its use.
   b. Its use should be limited to patients who have not experienced an adequate response with imiglucerase.
   c. It is administered via bolus intravenous injection.
   d. It is administered every 4 weeks.

CPE information
To obtain 2.0 contact hours of CPE credit (0.2 CEUs) for this activity, complete and submit the CPE exam online at www.pharmacist.com/education. A Statement of Credit will be awarded for a passing grade of 70% or better. You will have two opportunities to successfully complete the CPE exam. Pharmacists who successfully complete this activity before November 15, 2013, can receive credit.
Your Statement of Credit will be available online immediately upon successful completion of the CPE exam.
CPE instructions: Get your documentation of credit now! Completing a posttest at www.pharmacist.com/education is as easy as 1-2-3.
1. Go to Online CPE Quick List and click on the title of this activity.
2. Log in. APhA members enter your user name and password. Not an APhA member? Just click “Create one now” to open an account. No fee is required to register.
3. Successfully complete the CPE exam and evaluation form to gain immediate access to your documentation of credit.
   Live step-by-step assistance is available Monday through Friday 8:30 am to 5:00 pm ET at APhA Member Services at 800-237-APhA (2742) or by e-mailing InfoCenter@pharmacist.com.