New drugs approved in 2010

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This article briefly reviews select new drug entities approved by the Food and Drug Administration in 2010.

CARGLUMIC ACID (CARBAGLU)

Therapeutic use: Carglumic acid (1), a structural analog of N-acetylglutamate (NAG), is an allosteric activator of carbamoyl phosphate synthetase 1 (CPS 1) in liver mitochondria. NAG is the product of NAG synthase, a mitochondrial enzyme; CPS 1 is the first enzyme of the urea cycle, which converts ammonia into urea. Carglumic acid acts as a replacement for NAG in patients with NAG synthase deficiency by activating CPS 1. It is indicated for both acute and chronic hyperammonemia due to the deficiency of the hepatic enzyme NAG synthase.

Recommended dosage: The recommended initial dose for acute hyperammonemia is 100 to 250 mg/kg/day rounded to the nearest 100 mg and divided into 2 to 4 doses. Concomitant administration of other ammonia-lowering therapies is recommended. Dosing should be titrated based on individual patient plasma ammonia levels and clinical symptoms. Tablets should not be swallowed whole or crushed; each tablet should be dispersed in a minimum of 2.5 mL of water and taken immediately. Carglumic acid is available as 200-mg tablets.

Drug interactions: No drug interaction studies have been performed.

Adverse reactions: Effects most commonly associated with therapy include vomiting, abdominal pain, pyrexia, tonsillitis, anemia, ear infection, diarrhea, nasopharyngitis, and headache.

Other comments: Treatment with carglumic acid should be initiated by a physician experienced in metabolic disorders. Before opening the bottle, tablets should be refrigerated at 2° to 8°C; after opening the bottle, tablets should be kept at room temperature labeled with an expiration of 1 month.

CEFTAROLINE (TEFLARO)

Therapeutic use: Ceftaroline fosamil (2–6) is a cephalosporin antibacterial prodrug approved for the treatment of acute bacterial skin and skin structure infections (SSSIs) and community-acquired bacterial pneumonia in adults. Ceftaroline is the first cephalosporin active against resistant gram-positive pathogens. Ceftaroline is indicated to treat SSSIs caused by susceptible

Table 1. Recommended ceftaroline dosage adjustment in patients with renal impairment*

Estimated CrCl (mL/min) [†]	Recommended intravenous dose
>50	600 mg (over 1 hour) every 12 hours (no dosage adjustment necessary)
30–50	400 mg (over 1 hour) every 12 hours
15–30	300 mg (over 1 hour) every 12 hours
<15 including hemodialysis	200 mg (over 1 hour) every 12 hours [‡]

*Adapted from Teflaro product information (2).

[†]Creatinine clearance (CrCl) estimated using the Cockcroft-Gault formula.

[‡]Ceftaroline should be administered after hemodialysis on hemodialysis days.

isolates of the following microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *K. oxytoca*. Ceftaroline covers susceptible isolates of the following microorganisms that may cause community-acquired pneumonia: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *K. pneumoniae*, *K. oxytoca*, and *E. coli*. Ceftaroline's activity against methicillin-resistant *Staphylococcus aureus* is attributed to its high-affinity binding to penicillin-binding protein (PBP) 2a and more efficient inhibition of the biochemical activity of PBP 2a than β -lactams currently available.

Recommended dosage: The recommended dose of ceftaroline is 600 mg administered intravenously over 1 hour every 12 hours. The recommended treatment duration is 5 to 14 days for SSSIs and 5 to 7 days for community-acquired pneumonia; however, therapy duration should be individualized based on severity, site of infection, and the patient's clinical and bacteriological progress. Dosing should also be individualized based

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on renal function (*Table 1*). Ceftaroline is available as powder for reconstitution in 400-mg and 600-mg vials.

Drug interactions: The use of ceftaroline with other drugs has not been extensively studied.

Adverse reactions: The most common adverse reactions associated with ceftaroline are diarrhea, nausea, and rash. As with other cephalosporins, patients using ceftaroline are at risk for the development of an anaphylactic reaction and *Clostridium difficile*-associated diarrhea.

Other comments: Seroconversion from a negative to a positive direct Coombs' test result occurred in approximately 10% of the phase 3 study population. If anemia develops during or after treatment with ceftaroline, drug-induced hemolytic anemia should be ruled out.

COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (XIAFLEX)

Therapeutic use: Collagenase clostridium histolyticum (7, 8) is indicated for the treatment of Dupuytren's contracture with a palpable cord in adults. Dupuytren's disease is a fibroproliferative disorder of unknown etiology affecting the hand that often results in shortening and thickening of the palmar fascia, leading to permanent and irreversible flexion contracture of the digits. Collagenases are proteinases that are able to hydrolyze collagen in its native conformation under physiological conditions, resulting in lysis of collagen deposits. Injection of collagenase clostridium histolyticum into a Dupuytren's cord, which is composed mostly of collagen, may result in enzymatic disruption of the cord and contracture relief.

Recommended dosage: Collagenase clostridium histolyticum is dosed at 0.58 mg per injection, with the powder reconstituted using differing volumes of diluents based on whether the affected joint is a metacarpophalangeal joint or a proximal interphalangeal joint. Approximately 24 hours after injection, a finger extension procedure should be performed to facilitate cord disruption; if after 4 weeks the contracture remains, the cord may be reinjected with collagenase and the finger extension procedure may be repeated. Collagenase clostridium histolyticum is available as lyophilized powder in a 0.9-mg vial, which is accompanied by the sterile diluent to be used for reconstitution.

Drug interactions: Cautious use of injectable collagenase in patients who have received anticoagulants or platelet inhibitors (except aspirin up to 150 mg daily) is required, as efficacy and safety with concomitant use is unknown. With no detectable levels of injectable collagenase in plasma for up to 30 days after administration, other interactions are unlikely.

Adverse reactions: The most common adverse effects associated with the use of collagenase clostridium histolyticum include swelling of the injected hand, contusion, injection site reaction, injection site hemorrhage, and pain in the injection site hand. Injection of collagenase into collagen-containing structures such as tendons or ligaments of the hand may result in damage to those structures and possible permanent injury, such as tendon rupture or ligament damage. Therefore, collagenase should be injected only into the collagen cord, and care should be taken to avoid injecting it into tendons, nerves, blood vessels, or other collagen-containing structures of the hand.

Additionally, anaphylaxis is a potential reaction that health care providers should be prepared to treat.

Other comments: Collagenase clostridium histolyticum should be administered by a health care provider experienced in injection procedures of the hand and in the treatment of patients with Dupuytren's contracture. The reconstituted collagenase solution may be kept at room temperature for up to 1 hour or refrigerated at 2° to 8°C for up to 4 hours; the product should be at room temperature for administration.

DABIGATRAN (PRADAXA)

Therapeutic use: The direct thrombin inhibitor dabigatran (9, 10) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Thrombin enables the conversion of fibrinogen into fibrin in the coagulation cascade; inhibition of thrombin helps to prevent the development of a thrombus. Dabigatran is able to effectively inhibit both free and clot-bound thrombin and thrombin-induced platelet aggregation. Dabigatran is one of two orally available anticoagulants, the other being warfarin. Warfarin has a narrow therapeutic index, requiring intensive monitoring, and has extensive drug-drug and drug-food interactions. Dabigatran has fewer drug-drug interactions and does not require intensive monitoring; however, there is no specific antidote for dabigatran in patients who may experience major bleeding.

Recommended dosage: Dabigatran should be dosed at 150 mg twice daily. Dosage adjustment is required in renal impairment; patients with a creatinine clearance of 15 to 30 mL/min should receive 75 mg twice daily. When converting from a parenteral anticoagulant to dabigatran, bridge therapy is not necessary; dabigatran should be started 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug. Dabigatran is available as 75-mg capsules.

Drug interactions: Dabigatran is a substrate of P-glycoprotein (P-gp); plasma concentrations of dabigatran may be affected by inhibitors or inducers of P-gp. Concomitant use with P-gp inducers (specifically rifampin) should be avoided. In general, concomitant use with P-gp inhibitors does not require dose adjustments. Use with other anticoagulants or thrombolytic agents leads to an increased risk of bleeding.

Adverse reactions: Gastritis-like symptoms and bleeding are the most common adverse reactions. Dabigatran is contraindicated in patients with active bleeding.

Other comments: When possible, dabigatran should be temporarily discontinued before invasive surgical procedures and then promptly restarted afterwards.

DALFAMPRIDINE (AMPYRA)

Therapeutic use: The potassium channel blocker dalfampridine (11) is used to improve walking, measured by walking speed, in patients with multiple sclerosis (MS). The percentage of dalfampridine recipients with at least a 10%, 20%, or 30% increase in walking speed from baseline was significantly higher compared with placebo recipients.

Recommended dosage: The recommended and maximum dose of dalfampridine is 10 mg twice daily with or without food. Dalfampridine is contraindicated in patients with a creatinine clearance of ≤ 50 mL/min. It is available as a 10-mg tablet.

Drug interactions: No significant drug interactions with dalfampridine have been identified. In vitro, dalfampridine is not an inducer or inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Dalfampridine is not likely to affect the pharmacokinetics of drugs that are substrates of these enzymes. Further, dalfampridine is neither a substrate nor an inhibitor of P-gp.

Adverse reactions: The most common adverse reactions MS patients experience with dalfampridine treatment include urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, MS relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain. At doses of 20 mg twice daily, an increased incidence of seizures was noted; dalfampridine is contraindicated in patients with a history of seizures.

DENOSUMAB (PROLIA, XGEVA)

Therapeutic use: Denosumab (12, 13) is a monoclonal antibody directed against the receptor activator of nuclear factor kappa-beta ligand (RANKL). Denosumab prevents RANKL from activating its receptor, RANK, on osteoclast surfaces and their precursors. Prevention of this interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone. Denosumab has been approved under the brand name Prolia for the treatment of postmenopausal women with osteoporosis at high risk for fracture and under the brand name Xgeva for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

Recommended dosage: Prolia is supplied as a 1-mL prefilled syringe containing a solution of 60 mg/mL to be administered subcutaneously every 6 months in the specified patient population. Xgeva is supplied as a 1.7-mL prefilled syringe containing 70 mg/mL (120 mg/syringe) to be administered subcutaneously every 4 weeks in the specified patient population.

Drug interactions: There have been no formal studies regarding drug-drug interactions with denosumab.

Adverse reactions: The most common adverse reactions involving denosumab include back pain, extremity pain, hypercholesterolemia, musculoskeletal pain, and cystitis. More severe events that have been associated with denosumab use include hypocalcemia, infection, dermatological reaction, osteonecrosis of the jaw, and oversuppression of bone turnover. Patients taking denosumab should be instructed to take 1000 mg of calcium daily and at least 400 IU vitamin D daily to avoid hypocalcemia.

Other comments: Denosumab should be protected from light and refrigerated (2° to 8°C) prior to use. The product must be used within 14 days after removal from refrigeration.

HYDROMORPHONE EXTENDED RELEASE (EXALGO)

Therapeutic use: Exalgo is an extended-release oral formulation of hydromorphone (14) indicated for the management of

Table 2. Approximate conversion ratios to Exalgo*

Previous oral opioid	Approximate equivalent oral dose (mg)	Oral conversion ratio
Hydromorphone	12	1
Codeine	200	0.06
Hydrocodone	30	0.4
Methadone [†]	20	0.6
Morphine	60	0.2
Oxycodone	30	0.4
Oxymorphone	20	0.6

*Adapted from Exalgo product information (14).

[†]Conversion from methadone requires very close patient monitoring.

moderate to severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time. Patients are considered opioid tolerant if they are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for a week or longer. Exalgo is not intended for use as an as-needed analgesic or in the management of acute or postoperative pain.

Recommended dosage: When initiating treatment with Exalgo, health care providers need to consider the daily dose, potency, and specific characteristics of the opioid the patient had previously been taking, as well as the patient's degree of opioid tolerance, age, general condition, and medical status. This new extended-release formulation of hydromorphone is available as 8-mg, 12-mg, and 16-mg tablets. Table 2 shows the conversion from the current oral opioid therapy to hydromorphone.

Drug interactions: As with other opioid analgesics, Exalgo is not recommended to be used in combination with other central nervous system depressants (including alcohol), monoamine oxidase inhibitors, or opioid antagonists. Concomitant use with anticholinergics could lead to an increased risk of urinary retention and severe constipation, which may lead to paralytic ileus. Additionally, data suggest that hydromorphone in clinically relevant concentrations does have a minimal potential to inhibit the activity of human hepatic CYP450 enzymes including CYP1A2, 2C9, 2C19, 2D6, 3A4, and 4A11; care should be taken, as Exalgo may increase concentrations of drugs metabolized via the aforementioned enzymatic pathways.

Black box warning: Hydromorphone has a high potential for abuse and is classified as a schedule II controlled substance. Exalgo is only to be used in opioid-tolerant patients due to the high risk of fatal respiratory depression in an overdose situation. Tablets should be swallowed whole to allow for slow release and absorption of hydromorphone. Accidental consumption may lead to fatal overdose, especially in children.

Adverse reactions: Consistent with others in its class, hydromorphone's adverse effects include respiratory depression, hypotensive effects, gastrointestinal effects, cardiac arrest, head injury, and increased intracranial pressure.

Other comments: Exalgo is contraindicated in opioid non-tolerant patients, patients with impaired pulmonary function, and patients with paralytic ileus.

LIRAGLUTIDE (VICTOZA)

Therapeutic use: Liraglutide (15–19) is an incretin mimetic that acts as an agonist at the glucagon-like-peptide-1 (GLP-1) receptor; it is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Four 26-week trials with liraglutide as add-on therapy have been conducted; treatment protocols included liraglutide in combination with metformin, glimepiride, metformin plus glimepiride, and metformin plus rosiglitazone. In each of these trials, treatment with liraglutide resulted in improvements to hemoglobin A1C and fasting plasma glucose when compared with placebo. In addition, liraglutide given in combination with certain medications may contribute to weight loss.

Recommended dosage: Initial dosing should be 0.6 mg per day for 1 week to reduce gastrointestinal symptoms; this dose is not effective for glycemic control. The dose should be increased to 1.2 mg per day and can be increased further to 1.8 mg per day to achieve acceptable glycemic control. Liraglutide should be administered subcutaneously in the abdomen, thigh, or upper arm and can be given at any time during the day, independent of meals. Liraglutide is supplied in a prefilled pen as an 18 mg/3 mL solution for injection.

Drug interactions: Liraglutide causes a delay of gastric emptying and thus has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, liraglutide did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Serious hypoglycemia can occur when liraglutide is used with a sulfonylurea; the sulfonylurea dose may need to be lowered upon initiation of liraglutide.

Black box warning: Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in rodents; the existence of similar effects in humans is still unknown. Use of liraglutide in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2 is contraindicated.

Adverse reactions: The most common adverse reactions are headache, nausea, diarrhea, and anti-liraglutide antibody formation. In clinical trials, more cases of pancreatitis occurred among patients receiving liraglutide than comparators. If pancreatitis is suspected, liraglutide should be discontinued.

Other comments: Liraglutide should be stored in the refrigerator (2° to 8°C) until first use. After first use it has a beyond-use date of 30 days, either refrigerated or at room temperature (15° to 30°C). Liraglutide should be protected from extreme temperatures and sunlight.

LURASIDONE (LATUDA)

Therapeutic use: The atypical antipsychotic lurasidone (20) is approved for use in schizophrenia. Although the exact mechanism of lurasidone has not been determined, modulation of central dopaminergic and serotonergic activity is

thought to be the mechanism by which atypical antipsychotics are able to reduce the positive and negative symptoms of schizophrenia.

Recommended dosage: The recommended dose is 40 mg once daily, with a maximum daily dose of 80 mg. Lurasidone should be taken with food. It is available as 40-mg and 80-mg tablets.

Drug interactions: Lurasidone is highly protein bound and is metabolized primarily via the CYP3A4 pathway. Concomitant administration with either strong inducers (e.g., rifampin) or inhibitors (e.g., ketoconazole) of CYP3A4 is contraindicated.

Black box warning: Due to the increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) seen in elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs, lurasidone is not approved for the treatment of patients with dementia-related psychosis. Studies indicate that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

Adverse reactions: Common adverse reactions include somnolence, akathisia, nausea, parkinsonism, and agitation. The following adverse events are possible with all atypical antipsychotics, including lurasidone, and should be managed and monitored as clinically appropriate: neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, hyperglycemia and diabetes mellitus, dyslipidemia, weight gain, hyperprolactinemia, leukopenia, neutropenia, agranulocytosis, orthostatic hypotension and syncope, seizures, and potential for cognitive and motor impairment.

Other comments: Lurasidone should be taken with a minimum of 350 calories of food.

PEGLOTICASE (KRYSTEXXA)

Therapeutic use: Pegloticase (21–23) is a pegylated enzyme specific for uric acid. It is approved for use in patients with chronic gout refractory to other treatments. Pegloticase decreases uric acid concentrations by converting uric acid into allantoin, a benign metabolite that is easily excreted in the urine. Unfortunately, anti-pegloticase antibody development is high with use of pegloticase, and infusion reactions and hypersensitivity may limit use.

Recommended dosage: The recommended dosing for adults is 8 mg, given as an intravenous infusion every 2 weeks. Pegloticase should only be administered by intravenous infusion over no less than 120 minutes via gravity feed, syringe-type pump, or infusion pump. Pegloticase is supplied as a 1-mL sterile concentrate for dilution containing 8 mg of pegloticase protein, expressed in uricase protein amounts.

Drug interactions: No drug interaction studies have been performed. Anti-pegloticase antibodies appear to bind to the PEG portion of the drug; thus, the potential for binding with other pegylated products exists. The clinical implications are currently unknown.

Black box warning: Anaphylaxis and infusion reactions have been reported to occur during and after administration of pegloticase; therefore, the drug should only be administered

in a health care setting by a health care provider equipped to handle such reactions.

Adverse reactions: The most common adverse reactions are gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting. In premarketing clinical trials, anaphylaxis occurred in 6.5% of patients treated with pegloticase 8 mg every 2 weeks compared to none of the placebo patients, and infusion reactions occurred in 26% vs 5%, respectively.

Other comments: Use of pegloticase is not recommended for the treatment of asymptomatic hyperuricemia. Patients receiving pegloticase should be pretreated with an antihistamine and corticosteroid. Pegloticase should be stored in the carton and maintained under refrigeration between 2° to 8°C prior to preparation. The product should be protected from light, agitation, and freezing temperatures.

TESAMORELIN (EGRIFTA)

Therapeutic use: The growth hormone releasing factor tesamorelin (24–28) is indicated for lipodystrophy in HIV-infected patients. Lipodystrophy is characterized by adipose tissue redistribution and certain metabolic disorders including hypercholesterolemia and insulin resistance. Long-term highly active antiretroviral therapy exposure, particularly the combination of lopinavir and ritonavir, has the potential to lead to the development of dyslipidemia and lipodystrophy syndrome.

Recommended dosage: Recommended dosing for tesamorelin is 2 mg injected subcutaneously once daily. Tesamorelin is supplied in a kit for subcutaneous injection containing 1-mg vials of tesamorelin and additional vials containing the reconstitution diluents (sterile water for injection). The drug should be injected into the skin of the abdomen.

Drug interactions: Data suggest that growth hormone may alter the clearance of cytochrome P450-metabolized drugs; since tesamorelin stimulates growth hormone, patients receiving tesamorelin and compounds metabolized by CYP450 should be carefully monitored. Also, patients receiving glucocorticoids may require increased maintenance or stress dosages after initiation of tesamorelin.

Adverse reactions: The most commonly reported adverse reactions associated with tesamorelin are arthralgia, injection site erythema, injection site pruritus, extremity pain, peripheral edema, and myalgia.

Other comments: The reconstituted tesamorelin solution should be injected immediately. Nonreconstituted vials should

Table 3. Dose adjustments for tocilizumab*

Category	Laboratory values	Recommendation
Liver enzymes	>1 to 3 times ULN	Modify concomitant DMARDs if appropriate. For persistent increases in this range, reduce tocilizumab dose to 4 mg/kg or interrupt tocilizumab until liver transaminases have normalized.
	>3 to 5 times ULN	Interrupt tocilizumab dosing until <3 times ULN and follow recommendations above for >1 to 3 times ULN. For persistent increases >3 ULN, discontinue tocilizumab.
	>5 times ULN	Discontinue tocilizumab.
Absolute neutrophil count	1000	Maintain dose.
	500–1000	Interrupt tocilizumab dosing. When ANC is >1000 cells/mm ³ , resume tocilizumab at 4 mg/kg and increase to 8 mg/kg as clinically appropriate.
	<500	Discontinue tocilizumab.
Platelet level	50,000–100,000	Interrupt tocilizumab dosing. When platelet count is >100,000 cells/mm ³ , resume tocilizumab at 4 mg/kg and increase to 8 mg/kg as clinically appropriate.
	<50,000	Discontinue tocilizumab.

*Adapted from Actemra product information (29).

ULN indicates upper limit of normal; DMARDs, disease-modifying antirheumatic drugs.

be stored in the refrigerator (between 2° and 8°C) and protected from light. The reconstitution diluents should be stored at room temperature.

TOCILIZUMAB (ACTEMRA)

Therapeutic use: Tocilizumab (29) is an interleukin-6 (IL-6) inhibitor indicated for the treatment of rheumatoid arthritis in patients in whom one or more tumor necrosis factor inhibitors have failed. Tocilizumab exerts its effects in the serum and synovial fluid, where elevated IL-6 concentrations tend to occur in patients with rheumatoid arthritis. Additionally, elevated IL-6 concentrations are associated with disease activity and joint damage. Tocilizumab can be given independently or concomitantly with methotrexate or other disease-modifying antirheumatic drugs.

Recommended dosage: Initial dosing for tocilizumab is 4 mg/kg given as a 1-hour intravenous infusion every 4 weeks. The dose may be increased, based on response to 8 mg/kg intravenously every 4 weeks. Doses >800 mg per infusion are not recommended. Tocilizumab is available as single-use vials in the following strengths: 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL. Tocilizumab dosing should be adjusted as a result of certain dose-related laboratory changes; see *Table 3* for a summary.

Drug interactions: Tocilizumab has the potential to affect expression of multiple CYP enzymes. The formation of CYP450 enzymes may be suppressed by increased concentrations of cytokines such as IL-6 during chronic inflammation; as an IL-6 inhibitor, tocilizumab is expected to normalize the formation of these CYP450 enzymes. Care should be taken when using tocilizumab in combination with CYP3A4 substrate drugs.

Tocilizumab should not be administered concurrently with live vaccines.

Black box warning: Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving tocilizumab. Patients should be regularly monitored for tuberculosis for the duration of treatment.

Adverse reactions: The most common adverse reactions associated with tocilizumab include upper respiratory tract infections, nasopharyngitis, headache, hypertension, and increased alanine transaminase levels.

Other comments: Tocilizumab should not be administered if the patient is experiencing an active infection, including a localized infection. Tocilizumab must be refrigerated and not frozen. Vials must be protected from light by storage in their original package until time of use.

VELAGLUCERASE ALFA (VPRIV)

Therapeutic use: Velaglucerase alfa (30–32) is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy for pediatric and adult patients with type 1 Gaucher disease. Gaucher disease is caused by a deficiency of glucocerebrosidase, which helps the body metabolize glucocerebroside, a fatty material. Glucocerebroside can build up to harmful levels in the liver, spleen, lungs, bone marrow, and brain. This accumulation of fatty material in tissues interferes with the normal functioning of the body's organs and may cause organ enlargement and bone pain. Velaglucerase alfa is produced by gene activation technology in a human fibroblast cell line and, unlike current glucocerebrosidase moieties, has the same amino acid sequence as the naturally occurring human enzyme. The safety and efficacy of velaglucerase alfa have been established in children 4 years and older.

Recommended dosage: Velaglucerase should be dosed at 60 units/kg infused intravenously over 60 minutes every other week. Dosage adjustments, more specifically decreases in dose, can be made based on achievement and maintenance of each patient's therapeutic goals. Velaglucerase is supplied as a lyophilized powder to be reconstituted and diluted for infusion; it is available in 200-unit and 400-unit single-use vials.

Drug interactions: No studies have been done regarding drug-drug interactions with velaglucerase.

Adverse reactions: The most common adverse reactions associated with velaglucerase are infusion-related reactions (i.e., headache, dizziness, abdominal pain, nausea, back pain, joint pain, upper respiratory tract infection, prolongation of activated partial thromboplastin time, fatigue/asthenia, and pyrexia). Additionally, hypersensitivity can occur with velaglucerase alfa, and care should be exercised.

Other comments: Velaglucerase should be stored protected from light in a refrigerator at 2° to 8°C. Reconstituted velaglucerase should be used immediately. If immediate use is not possible, the product may be stored for up to 24 hours in a refrigerated location.

Table 4. Chemotherapeutic agents approved in 2010*

Generic name	Brand name	Indication
Cabazitaxel	Jevtana	Treatment of prostate cancer in combination with prednisone in hormone-refractory patients previously treated with a docetaxel-containing regimen.
Eribulin mesylate	Halaven	Treatment of metastatic breast cancer in patients who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.
Sipuleucel-T	Provenge	Treatment of asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer.

*From product information (33–35).

CHEMOTHERAPEUTIC AGENTS

Table 4 provides information regarding new chemotherapeutic agents and their approved indications.

1. Carbaglu® (carglumic acid) tablets for dispersion [product information]. Memphis, TN: Accredo Health Group Inc, Nov 2010.
2. Teflaro™ (ceftaroline fosamil) powder for intravenous injection [product information]. St. Louis, MO: Forest Pharmaceuticals Inc, Oct 2010.
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7. Xiaflex™ (collagenase clostridium histolyticum) powder for intralesional injection [product information]. Malvern, PA: Auxilium Pharmaceuticals Inc, Feb 2010.
8. Shih B, Bayat A. Scientific understanding and clinical management of Dupuytren disease. *Nat Rev Rheumatol* 2010;6(12):715–726.
9. Pradaxa® (dabigatran etexilate mesylate) capsules for oral use [product information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc, Oct 2010.
10. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361(12):1139–1151.
11. Ampyra™ (dalfampridine) Extended Release Tablets, for oral use [product information]. Hawthorne, NY: Acordia Therapeutics Inc, Jan 2010.
12. Prolia™ (denosumab) injection for subcutaneous use [product information]. Thousand Oaks, CA: Amgen Inc, June 2010.

13. Xgeva™ (denosumab) injection for subcutaneous use [product information]. Thousand Oaks, CA: Amgen Inc, Nov 2010.
14. Exalgo® (hydromorphone HCl) Extended-Release Tablets, CII [product information]. Hazelwood, MO: Mallinckrodt Brand Pharmaceuticals Inc, Apr 2010.
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