Drugs on the horizon

By Mark S. Johnson, PharmD, BCPS
The FDA approved roughly 34 new drugs and biologics in 2013. Some of the notable approvals from 2013 included eight new cancer treatments, such as several kinase inhibitors for various cancer types (afatinib, ibrutinib, dabrafenib, and trametinib), four new diabetes drugs, including a new class of drugs (sodium-glucose cotransporter 2 inhibitors—canagliflozin), a new oral drug for multiple sclerosis (dimethyl fumarate), new agents for hepatitis C (simeprevir, sofosbuvir), and more.¹ The forecast for drug development and approval into 2014 looks good. Predictions for the future include continuing focus on safety in the development process; continued development of oncology drugs, hepatitis C drugs, and diabetes drugs; orphan drug development; and increased development of biologics and specialty drugs for specific populations through the use of pharmacogenomics.²

This article provides a glimpse into the future and highlights significant drugs on the horizon in the United States for 2014. It includes drugs that are unique based on mechanism of action or other properties when compared with drugs already on the U.S. market for a particular disease state, are farthest along in Phase III clinical trials, and/or were very recently FDA approved as of the publication of this article.

Unless otherwise specified, the information in the following summaries applies to adults, not children. Consult a pharmacist or the package insert for information about each drug’s safety during pregnancy and breastfeeding. Consult a pharmacist, the package insert, or a comprehensive and current drug reference for more details on precautions, drug interactions, and adverse reactions for all of these drugs.

**Insulin human [rDNA origin]**

Insulin human [rDNA origin] is an ultra rapid-acting mealtime insulin
that’s manufactured in powder form for inhalation and is administered through an inhaler to improve glycemic control in adult patients with type 1 or type 2 diabetes. It should be taken at the start of a meal and will dissolve immediately upon inhalation to the lungs with peak insulin serum levels achieved within 12 to 15 minutes. This is faster than both subcutaneous rapid-acting insulin analogues (45 to 90 minutes) and subcutaneous regular human insulin (90 to 150 minutes).3,4

A resubmission of a new drug application (NDA) was submitted to the FDA in October 2013 based on the results of two recent Phase III trials. In the first trial, the primary efficacy endpoint was met demonstrating superiority to metformin (first-line therapy for diabetes), with or without a second or third oral medication (combination therapy). Patients taking insulin human [rDNA origin] had a decrease in mean hemoglobin A1c levels of 0.82% compared with a 0.42% decrease in patients taking metformin. In the second study, insulin human [rDNA origin] was compared with insulin aspart, a fast-acting insulin, and researchers determined that insulin human [rDNA origin] is noninferior to insulin aspart.5,6

Albiglutide
Albiglutide is a glucagon-like peptide (GLP) 1 agonist that’s under investigation as a once-weekly drug for adults with type 2 diabetes. It has been studied in eight Phase III trials (Harmony 1-8) in over 5,000 patients. In a 52-week trial comparing albiglutide with sitagliptin in patients with type 2 diabetes and renal impairment (Harmony 8), significant reductions in hemoglobin A1c levels were demonstrated at 26 weeks (8.08% for albiglutide and 8.22% for sitagliptin). Significantly greater weight loss (0.79 kg [1.74 lbs] versus 0.19 kg [0.42 lbs], respectively) was also noted. A decision from the FDA is forthcoming in 2014 following the submission of the Biologics License Application in January.5,6

Dulaglutide
Dulaglutide is a GLP 1 agonist that’s under investigation as a once-weekly drug for adults with type 2 diabetes. It has been studied in numerous Phase III trials (AWARDS 1-5), and has had positive results. In AWARD 2, dulaglutide was compared with insulin glargine and demonstrated significant reductions in hemoglobin A1c levels at 52 weeks in patients on metformin and glimepiride. In AWARD 4, dulaglutide combined with insulin lispro yielded significant reductions in hemoglobin A1c versus insulin glargine combined with insulin lispro at 26 weeks.6 A new study (REWIND) is currently ongoing to assess cardiovascular and other serious adverse drug reactions. The manufacturer is awaiting a decision from the FDA and hopes to market dulaglutide in 2014.4

Empagliflozin
Empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, is currently being investigated for the treatment of adults with type 2 diabetes. A similar drug, canagliflozin, was approved in 2013 as the first SGLT2 drug on the U.S. market. Empagliflozin phase III trials have enrolled over 14,500 patients worldwide. Some results were recently presented at the 49th European Association for the Study of Diabetes (EASD) Annual Meeting. Researchers presented data on 2,477 patients treated with empagliflozin (10 mg or 25 mg) for 24 weeks as monotherapy or as an add-on to metformin, metformin with sulphonylurea, or pioglitazone with or without metformin. At 24 weeks, empagliflozin demonstrated significant reductions in hemoglobin A1c and weight loss (1.63 kg [3.59 lbs] and 2.01 kg [4.43 lbs]) when compared with placebo.7

Results for 14,500 patients were recently presented at the American Diabetes Association’s 73rd Scientific Sessions, which noted dose-related (10 and 25 mg) significant reductions in hemoglobin A1c (0.62% to 0.68%), fasting plasma glucose (27.9 to 30.6 mg/dL), weight (1.8 kg [3.97 lbs] to 2 kg [4.41 lbs]), and BP. The manufacturer is awaiting a decision by the FDA and hopes to market empagliflozin in 2014.4,7,8

Dapagliflozin
Dapagliflozin is a SGLT2 inhibitor that’s being investigated for the treatment of adults with type 2 diabetes. Positive results were recently presented at the EASD annual meeting of Phase III trials as an add-on therapy to metformin plus sulphonylurea. Significant reductions in hemoglobin A1c, fasting plasma glucose, and body weight were noted at 24 weeks compared with placebo. Additionally, systolic BP improved at 8 weeks. The manufacturer is currently awaiting a decision from the FDA after an advisory committee recommended approval in December 2013. After originally filing an NDA in March 2011, an FDA advisory committee recommended against approval in July 2011 citing more data were needed to further investigate concerns with cancer (breast and bladder) and liver injury.2

Simeprevir
Simeprevir is a protease inhibitor recently approved by the FDA for
the treatment of chronic hepatitis C. It blocks a specific protein needed by the hepatitis C virus (HCV) to replicate. It’s the third FDA-approved protease inhibitor to treat chronic HCV infection, boceprevir and telaprevir were approved in 2011. Simeprevir is approved as part of a combination antiviral treatment regimen (peginterferon alfa and ribavirin) for adults with compensated liver disease in treatment-naive and treatment-experienced patients.

The safety and efficacy of simeprevir has been evaluated in five clinical trials in 2,026 treatment-naive and treatment-experienced patients. Simeprevir plus peginterferon alfa and ribavirin was compared with placebo plus peginterferon alfa and ribavirin in achieving sustained virologic response (no HCV detected in the blood at least 12 weeks after completing treatment). Of the treatment-naive patients receiving simeprevir, 80% achieved a sustained virologic response compared with 50% in the placebo-combined group. In one of the studies with treatment-experienced patients whose infection returned (prior relapse), 79% of simeprevir-treated patients achieved sustained virologic response compared with 37% of patients in the placebo group.

Safety and efficacy in treatment-experienced participants (including prior relapsers, partial responders, and null responders) showed improved response with simeprevir. A reduction in efficacy, however, was noted in patients with the genotype 1a HCV with an NS3 Q80K polymorphism. It’s recommended that healthcare providers screen patients for this strain before starting treatment with simeprevir. The most common adverse drug reactions were rash, pruritis, nausea, and photosensitivity.

**Sofosbuvir**
Sofosbuvir was recently approved by the FDA for the treatment of chronic HCV. Sofosbuvir is an oral nucleotide analogue inhibitor of the HCV NS5B polymerase enzyme, which is needed for HCV replication. Sofosbuvir’s effectiveness was demonstrated in six clinical trials of 1,947 participants who were treatment-naive or treatment-experienced, including participants coinfected with HCV and HIV. Sofosbuvir showed efficacy in treating multiple types of HCV, in those who couldn’t tolerate or take an interferon-based treatment regimen, and in participants with liver cancer awaiting liver transplantation.

The most common adverse drug reactions with sofosbuvir and ribavirin were fatigue and headache; with sofosbuvir, ribavirin, and peginterferon alfa the most common adverse reactions were headache, insomnia, anemia, nausea, and fatigue. The drug is FDA approved for two chronic HCV indications: in combination with pegylated interferon and ribavirin for treatment-naive adults with genotype 1 and 4 infections, and in combination with ribavirin for adults with genotypes 2 and 3 infection. This is the first approval of an interferon-free regimen for the treatment of chronic HCV. Other drugs in the pipeline for HCV include daclatasvir (an NS5A inhibitor that blocks the NS5A protein needed for HCV replication), asunaprevir (a protease inhibitor), and ledipasvir (an NS5A inhibitor).

**Dalbavancin**
Dalbavancin is an antibiotic for the treatment of patients with **absssi** and hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia. It’s a once-daily oxazolidinone for the treatment of serious Gram-positive infections, including MRSA. Similar to the oxazolidinone linezolid, it’s being evaluated as both oral and I.V. therapy. Data from two Phase III trials (ESTABLISH 1 and ESTABLISH 2) with 1,333 patients revealed that tedizolid 200 mg once daily for 6 days was noninferior to linezolid 600 mg twice daily in the treatment of **absssi**. The most common adverse drug reactions were gastrointestinal (nausea, vomiting, diarrhea), but these reactions were lower with tedizolid. The drug has been granted Fast Track status under the Generating Antibiotic Incentives Now Act, which was created to assist in the development and approval of new antibiotics.

**Tedizolid phosphate**
Tedizolid is an antibiotic for the treatment of patients with MRSA and hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia. It’s a once-daily oxazolidinone, which is noninferior to linezolid. Similar to the oxazolidinone linezolid, it’s being evaluated as both oral and I.V. therapy. Data from two Phase III trials (DISCOVER 1, DISCOVER 2, VER001-9) have been conducted and submitted to the FDA. An NDA has been submitted to the FDA by the manufacturer and has been accepted for priority review with a decision scheduled on or before May 26, 2014.

**Droxidopa**
Droxidopa is being studied for the treatment of symptomatic neurogenic...
orthostatic hypotension (NOH). It’s an oral synthetic precursor of norepinephrine that’s converted to norepinephrine by decarboxylation in the central and peripheral nervous system.

NOH is a chronic neurogenic disorder caused by decreased norepinephrine release affecting patients with primary autonomic failure, including Parkinson disease. One adverse reaction is fainting, which can limit a person’s ability to perform routine daily activities that require standing or walking. Other adverse reactions include dizziness, lightheadedness, blurred vision, fatigue, and poor concentration.

Droxidopa has been available for years in Japan. It’ll be reviewed by the FDA in early 2014. It was previously granted Orphan Drug Designation for the treatment of NOH in patients with primary autonomic failure, dopamine-ß-hydroxylase deficiency, or nondiabetic autonomic neuropathy, and received Fast Track designation.2,13

**Tasimelteon**

Tasimelteon is a circadian rhythm regulator under investigation for the treatment of Non 24—a circadian rhythm disorder that affects many totally blind people. It’s characterized by the inability to synchronize (entrain) the body’s master clock with the 24-hour day-night cycle. Light normally resets the body’s master clock, but this doesn’t occur in patients with non-24, which affects the timing of the secretion of melatonin and cortisol. As a result, the sleep-wake cycle is disrupted, which impairs social and occupational activities.14

Tasimelteon is a dual melatonin receptor agonist with selective agonist activity at the MT1 and MT2 receptors. Tasimelteon resets the master body clock in the suprachiasmatic nucleus. Melatonin and cortisol rhythms are then entrained with the 24-hour day-night cycle. Tasimelteon is currently under FDA Priority Review as an Orphan Drug and has been recommended for approval by an FDA advisory committee.2,14

**Naloxegol**

Opioid-induced constipation is the most common adverse drug reaction caused by chronic opioid use. Opioids bind to opioid receptors (proteins) in the gastrointestinal tract causing constipation, increased fluid absorption, and decreased gastrointestinal motility. Roughly 50% of patients taking opioids for long-term pain develop opioid-induced constipation; about one-half of those patients are successfully treated with laxatives. Naloxegol is a peripherally acting mu-opioid receptor antagonist under investigation for opioid-induced constipation in adults with chronic noncancer-related pain. Naloxegol blocks opioid receptors in the gastrointestinal tract, not opioid receptors in the brain. It’s administered orally once daily and, if approved, would be the first such drug in its class.15

Phase III studies (KODIAC trials) have compared 12.5 and 25 mg doses with placebo in both short-term (12 week) and long-term (52 week) extensions.15 The long-term safety compared with usual care showed no significant differences in serious adverse events but several adverse reactions (abdominal pain, diarrhea, nausea, and headache) were more frequent with naloxegol. The primary endpoints for efficacy were met in this trial and the 25 mg dose (12.5 mg dose didn’t meet efficacy endpoints in one study).15

Several opioids are undergoing investigation for FDA approval, including:

- morphine and oxycodone, an opioid analgesic combination in development for the treatment of moderate-to-severe acute pain
- sufentanil sublingual microtablet system, a patient-activated, noninvasive analgesic system for the management of moderate-to-severe acute pain in hospitalized adults
- acetaminophen and oxycodone extended-release, an oral opioid analgesic for the management of moderate-to-severe acute pain
- naloxone and oxycodone, an opioid antagonist and opioid analgesic combination for management of chronic pain.2

**Vedolizumab**

Vedolizumab is a humanized monoclonal antibody being investigated for the treatment of moderate-to-severe Crohn disease and ulcerative colitis. It works differently than the current therapies on the market. Vedolizumab antagonizes the alpha 4 beta 7 integrin, inhibiting the binding of alpha 4 beta 7 to intestinal mucosal addressin cell adhesion molecule 1 (MAdCAM-1). In the gastrointestinal tract, MAdCAM-1 is expressed on blood vessels and lymph nodes.2,16,17 The alpha 4 beta 7 integrin is expressed on a subset of white blood cells. These cells help mediate the inflammatory process in Crohn disease and ulcerative colitis. These common types of inflammatory bowel disease can cause significant morbidity and are difficult to treat. Although there’s no known cause, researchers have found a relationship between genetics, the immune system, and environmental factors. The goal of treatment is to induce and maintain remission, or achieve extended periods of time when patients are symptom free.2,16,17

Four Phase III trials (GEMINI) have investigated vedolizumab in...
Umeclidinium/vilanterol
Umeclidinium/vilanterol is under investigation for the maintenance treatment of airflow obstruction in chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. It’s a combination long-acting muscarinic and long-acting beta 2 agonist administered once daily using an inhaler. If approved, umecclidinium/vilanterol will become the first once-daily dual bronchodilator available in the United States. It has been studied in over 6,000 COPD patients in clinical trials to date. Adverse drug reactions include headache, cough, upper respiratory tract infections, and cardiac ischemia. An FDA advisory committee has recommended the drug for approval; a final FDA decision is expected soon.²,¹⁸

Idelalisib
Indolent non-Hodgkin lymphoma is a group of slow-growing lymphomas that run a relapsing course after therapy and ultimately lead to life-threatening complications such as infections and bone marrow failure. Median survival from time of initial diagnosis is 8 to 10 years with follicular lymphoma, the most common form.

Idelalisib is an investigational, targeted, highly selective oral inhibitor of phosphoinositide 3-kinase (PI3K) delta, a protein needed for the activation, proliferation, and survival of B lymphocytes. B lymphocytes are white blood cells that produce antibodies. B-cell lymphomas make up the majority of non-Hodgkin’s lymphomas. PI3K delta signaling is hyperactive in many B-cell leukemias and lymphomas. Clinical trials support the use of idelalisib for patients with indolent non-Hodgkin lymphoma that’s refractory to rituximab and alkylating-agent-containing chemotherapy.¹⁹

A Phase II trial of 125 patients with indolent non-Hodgkin lymphoma refractory to rituximab and alkylating-agent-containing chemotherapy demonstrated an overall response rate of 53.6%, with a median response duration of 11.9 months at interim analysis. Median progression-free survival for all patients was 11.4 months and 89% of patients experienced lymph node shrinkage. The most common Grade ≥3 adverse drug reactions were diarrhea (10%), transaminase elevations (13%), and neutropenia (26%). Other idelalisib trials are ongoing and include patients with previously treated indolent non-Hodgkin lymphoma, chronic lymphocytic leukemia, and other hematologic malignancies.¹²

Ibrutinib
Chronic lymphocytic leukemia is the second most common form of adult leukemia. It’s a B-cell malignancy and is a slow-growing white blood cell cancer (lymphocytes). Chronic lymphocytic leukemia is a disease that mostly occurs in older adults and has a 5-year survival rate of 82%. Patients commonly receive multiple lines of treatment over the course of their disease. Mantle cell lymphoma is an aggressive B-cell type non-Hodgkin lymphoma. It usually occurs in older adults and begins in the lymph nodes, but can spread to other tissues. Average survival is also 5 years.

Ibrutinib was recently approved for previously treated mantle cell lymphoma and previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma. Ibrutinib is an inhibitor of an enzyme called Bruton tyrosine kinase (BTK), a mediator of B-cell survival by multiple signals (apoptosis, adhesion, cell migration, and homing).²⁰ Thus, BTK regulation helps to direct malignant B cells to lymphoid tissues, enhancing their survival. The effectiveness of ibrutinib alone or in combination with other treatments is being studied in several B-cell malignancies. Seven Phase III trials are ongoing and additional trials are planned.²⁰

Observing the trends
Drug development and approval continues to be robust and dynamic. Because medications are a significant part of a patient’s care, it’s important for nurse managers to keep up with these trends to plan for and provide the best patient care possible and empower clinical nurses to do the same. NM

REFERENCES


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