In This Issue

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Formulary Information

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Canagliflozin– A New Antidiabetic Medication

By: Marianna Fedorenko, Pharm.D.

Introduction: It is estimated that 25.8 million people in the United States have diabetes, which can result in over 100 billion dollars of direct medical costs.[1] Type 2 diabetes, which is characterized by defective insulin secretion, insulin resistance, and a progressive decline in beta cell function, is much more prevalent than Type 1 diabetes.[1,2] Type 2 diabetes treatment guidelines recommend metformin as initial therapy when lifestyle changes alone are deemed ineffective at meeting glycemic goals.[3] Alternative agents are used if patients have contraindications to or are intolerant to metformin or when monotherapy is insufficient. Common pharmacologic classes include: sulfonylureas, thiazolidinediones (TZD), glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidylpeptidase 4 (DPP-4) inhibitors, and/or insulin. Due to the progressive nature of the disease, combination therapy is often required to achieve glycemic targets. However, current therapy is limited by treatment-related adverse effects such as hypoglycemia, weight gain, edema, and an increased risk for cardiovascular complications.[4] Successful research efforts to design novel anti-diabetic medications led to the recent introduction of canagliflozin (Invokana®; Janssen Pharmaceutical) in March 2013, which is the first of its class of sodium-glucose co-transporter-2 (SGLT-2) inhibitors.[5]

Glucose Homeostasis and SGLT Transporters: This new class of antidiabetic medications targets the kidneys, which play a significant role in glucose homeostasis.[6] Blood glucose is renally regulated by gluconeogenesis, glomerular filtration, and subsequent reabsorption in the proximal convoluted tubules. Once glucose is freely filtered through the glomerulus, ap-

(Continued on page 2)

Hospital Consumer Assessment of Healthcare Providers and Systems

By: Cory McEwen, Pharm.D.

Introduction: The Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey, developed by the Centers for Medicare and Medicaid (CMS), is a survey designed to evaluate patients' perspectives of the care provided by hospitals during an inpatient admission. The HCAHPS survey is one component of value-based purchasing (VBP), a program authorized by the Affordable Care Act.[1] Under this program, hospital reimbursement from Medicare is dependent on the quality of care provided. The HCAHPS survey was implemented with three broad goals: 1) to standardize survey protocol, 2) to create incentives for hospitals to perform well, and 3) to enhance accountability.[2] These objectives are accomplished by requiring all hospitals to implement the same survey, directly linking HCAHPS scores to Medicare reimbursement, and publicly reporting results online (http://www.medicare.gov/hospitalcompare/search.html).

Measures: The HCAHPS survey is broken down into six summary measures, two individual items, and two global items. The summary measures include

(Continued on page 3)

(Continued from page 1)

proximately 99% is reabsorbed in the proximal convoluted tubule and less than 1% is renally excreted. Usually, glucosuria appears once the blood glucose threshold of 180 mg/100 mL is exceeded.[6,7] Sodium-glucose co-transporter-2, a co-transporter that facilitates glucose movement by help of sodium's electrochemical gradient, conducts 90% of filtered glucose transport from the tubule to adjacent epithelial cells.[6,7] Sodium-glucose co-transporter-1, another SGLT membrane protein, is responsible for 10% of tubular reabsorption and plays a primary role in intestinal glucose absorption.[6] Consequently, inhibiting SGLT-2 induces urinary glucose excretion (i.e., causes glucosuria), decreases serum glucose levels, and leads to calorie loss and potential weight loss. A number of agents with this mechanism of action have been evaluated in preclinical and clinical trials; a few include canagliflozin, dapagliflozin, sergliflozin, and remogliflozin etabonate.[6,7]

Canagliflozin: Canagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with Type 2 diabetes mellitus.[5] It has been studied as both monotherapy and add-on therapy in patients ineffectively controlled with combination therapy. In patients treated with canagliflozin, the HbA1c decreased by 0.8 to 1% from baseline. Interestingly, due to its increasing urinary glucose excretion, treatment-related effects such as hypotension and weight loss may also aid in management of other common co-morbidities, such as hypertension and obesity.[5,8,9] Safety concerns include hypotension, hyperkalemia, and renal impairment, especially in volume-depleted patients or those with pre-existing renal dysfunction.[5] The hypoglycemia risk is low as this agent does not act on insulin secretion, but it increases with concomitant sulfonylurea or insulin treatment. A unique adverse effect is the high rate of genital mycotic infections (e.g., vulvovaginal candidiasis, candidal balanitis, balanoposthitis) occurring in ~10% of female and ~4% of male patients. Recurrent infections are more likely in those with a prior history and who experience the initial event while taking canagliflozin. Symptoms generally resolve after topical and/or oral antifungal treatment. The recommended starting dose is 100 mg orally once daily taken before the first meal of the day.[5] Dose adjustments based on estimated glomerular filtration rate (eGFR) are required for patients with renal dysfunction (Table 1). Co-administration with UDP-Glucuronosyl Transferase (UGT) enzyme inducers (e.g., rifampin, phenytoin, phenobarbital, ritonavir) may decrease canagliflozin serum levels; dose increases should be considered only in patients with an eGFR > 60 mL/min/1.73 m^2 who need additional glycemic control.

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Table 1: Canagliflozin Dosage Recommendations[5]

eGFR (mL/min/1.73 m^2)/dialysis	Dose	Maximum Dose
>60	100 mg once daily	300 mg once daily*
45 - 60	100 mg once daily	100 mg once daily
<45	Not indicated/Discontinue	N/A
<30, end stage renal disease, or dialysis	Contraindicated	N/A

eGFR=estimated glomerular filtration rate N/A=not applicable

*Increase to 300 mg once daily if 100 mg is insufficient to meet glycemic goals or when co-administered with UGT enzyme inducers and additional glycemic control is required

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communication with doctors, communication with nurses, pain control during the hospital stay, responsiveness of the hospital staff, communication about medications, and discharge information provided. Two individual items assess patients' perception of the cleanliness and quietness of the hospital and two global measures address overall rating of the hospital and whether they would recommend the hospital to friends or family. Each measure contains two to three composite questions and is scored based on the percentage of time patients answer with a "top box" response (i.e., "always", "strongly agree"). The HCAHPS survey is designed to give the consumer information that is easier to interpret compared to clinical information, giving patients the ability to make an informed decision about where they receive their healthcare.

Eligibility: Any patient 18 years of age or older with a hospital stay of 24 hours or longer who is discharged from a medical, surgical, or maternity unit with a non-psychiatric diagnosis is eligible to receive an HCAHPS survey.[3] The survey is sent to a random selection of discharged patients from 48 hours to 6 weeks after discharge.[2]

Reimbursement: On October 1, 2012, HCAHPS scores began directly affecting Medicare reimbursement. For the fiscal year of 2013, 1% of all Medicare payments will be withheld from hospitals. These funds will then be re-allocated based on how well hospitals perform on the survey as well as other clinical measures. Hospitals performing well have the potential to receive increased reimbursement based on how their scores compared to other similar hospitals across the country. Initial analysis of 2012 data revealed that 1557 hospitals will receive additional payments in the fiscal year of 2013, and 1427 hospitals will receive less money.[4]

Outlook of Value Based Purchasing: The exact future of VBP is unknown, but it is certainly evolving. In the fiscal year of 2014, CMS is adding outcome measures including 30-day mortality for acute myocardial infarction, congestive heart failure, and pneumonia. In addition, CMS has established an annual increase of Medicare withholdings of 0.25%.[4] The VBP process will be continuously evaluated by CMS to best accomplish the desired outcomes of improved quality of care at a decreased cost.

Cleveland Clinic Pharmacy Initiatives: Many initiatives have been implemented by the Department of Pharmacy to help contribute to the organization's efforts of improving patient experience, including:

- Heart Failure Counseling
- Warfarin Education
- Discharge Counseling
- Medication Bedside Delivery
- Transplant Medication Action Plans
- Emergency Department Medication Reconciliation

The Department of Pharmacy is committed to improving patient experience and the quality of care provided at the Cleveland Clinic.

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Updates in Hepatitis C Therapy

By: Brian S. Hoffmaster, PharmD

Introduction: Prior to 2011, standard of care for hepatitis C virus (HCV) infections included peginterferon alfa and ribavirin administered for either 24 or 48 weeks, depending on HCV genotype.[1] Efficacy of this treatment is determined by the achievement of a sustained virologic response (SVR) which has been defined as undetectable plasma HCV ribonucleic acid (RNA) at 24 weeks after completion of therapy. Sustained virologic response is associated with reduced morbidity and mortality.[1,2] This combination therapy has been ≥80% effective for HCV genotypes 2 and 3, but only 40-50% effective for HCV genotype 1 (HCV1).[1] Since HCV1 is the most prevalent strain with the lowest response rate to standard therapy, new treatment modalities needed to be developed.[3] On May 23, 2011, boceprevir (Victrelis®; Merck & Co., Inc.) and telaprevir (Incivek™; Vertex Pharmaceuticals, Inc.) were approved by the Food and Drug Administration (FDA) for the treatment of chronic HCV1 in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or have not responded to previous therapy with peginterferon alfa and ribavirin.[4,5]

Mechanism of Action: Boceprevir and telaprevir are the first agents in their class, NS3/4A serine protease inhibitors, to be approved in combination with peginterferon alfa and ribavirin for use in HCV1.[1] These protease inhibitors are a sub-class of direct-acting antiviral (DAA) agents. They act by disrupting RNA replication and virion assembly effectively inhibiting HCV1 replication.

Efficacy: These agents have significantly improved SVR rates for HCV1. In patients who had not previously been treated for HCV1, the rates of SVR were as high as 66% and 75% with boceprevir and telaprevir, respectively.[4,5] The SVRs in patients who had previously relapsed with peginterferon alfa and ribavirin were 75% and 83% for boceprevir and telaprevir, respectively. Telaprevir was also studied in HCV1 patients previously treated with peginterferon alfa and ribavirin who had not responded to therapy and it produced a 29% SVR rate compared to a 5% SVR rate with standard peginterferon alfa and ribavirin therapy.[6] All comparisons to control groups in these trials were statistically significant favoring either boceprevir or telaprevir treatment groups.[4-6]

Guidelines versus FDA Indications: The significant improvement in SVR rates has led to the inclusion of these agents as standard therapy for HCV1 in the 2011 Update of Practice Guidelines for the Treatment of HCV1.[1] These guidelines give the highest class and level of evidence for recommending boceprevir or telaprevir in combination with peginterferon alfa and ribavirin for optimal HCV1 therapy in treatment-naïve patients (Class 1, Level A). Although controversial, therapy with boceprevir should be preceded by 4 weeks of lead-in therapy of peginterferon alfa and ribavirin alone in treatment-naïve patients. Therapy with telaprevir does not require a 4 week lead-in phase. Furthermore, the guidelines give a similar level of recommendation for boceprevir or telaprevir in combination with peginterferon alfa and ribavirin for HCV1 therapy in patients who had virologic relapse or were partial responders after a prior course of treatment with standard peginterferon alfa and ribavirin (Class 1, Level A). However, in the therapy of prior non-responders to standard peginterferon alfa and ribavirin, retreatment with telaprevir together with peginterferon alfa and ribavirin, is recommended with less well-established evidence (Class 2b, Level B). For response-guided therapy in which treatment is discontinued based on viral load levels at designated time intervals, boceprevir or telaprevir may be used for relapsers (Class 2a, Level B for boceprevir; Class 2b, Level C for telaprevir) and partial responders (Class 2b, Level B for boceprevir; Class 3, Level C for telaprevir) but not prior non-responders to standard peginterferon alfa and ribavirin due to limited supportive evidence (Class 3, Level C for both). It should be noted that in contrast to the guidelines, both drugs are FDA-approved for use in patients who failed previous standard therapy including non-responders.

Precautions and Adverse Effects: Neither agent should be used as monotherapy, and each must always be used with peginterferon alfa and ribavirin to avoid HCV resistance.[1] Boceprevir and telaprevir must be considered pregnancy risk category X, since they will always be coadministered with ribavirin, a pregnancy risk category X drug. Likewise, both agents are contraindicated for use in males whose female partners are pregnant.[4,5] The most commonly associated side effects of boceprevir are anemia and dysgeusia. Telaprevir is most commonly associated with rash, anemia, pruritis, nausea, and diarrhea.[1] Rarely (<1% of patients), telaprevir has been associated with Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), or Toxic Epidermal Necrolysis (TEN). Certain adverse effects, such as anemia, may warrant a dosage reduction for ribavirin as described in the boceprevir or telaprevir product labeling.[4,5]

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Drug Interactions: Both of these agents also require particular attention to concomitant therapy and the potential for drug interactions.[1,4,5] Several significant drug interactions, mainly involving metabolism medications metabolized through the cytochrome P450 (CYP450) 3A4 enzyme system. Please refer to the prescribing information and tertiary drug references, such as Lexi-Comp for more detailed information involving the many potential drug interactions for boceprevir or telaprevir. Each provider should review the relevant drug interaction information before initiating HCV1 therapy.[1,4,5] Boceprevir and telaprevir are contraindicated for concurrent use with drugs that induce CYP3A (specifically CYP3A4/5 for boceprevir) or drugs with narrow therapeutic indices which highly depend on those enzyme systems for clearance.[4,5]

Dosage and Administration: The recommended dose of telaprevir tablets is 750 mg (two 375-mg tablets) taken orally three times daily (7-9 hours apart) with food containing approximately 20 grams of fat.[5] Patients need to be aware that fat content is important for telaprevir absorption, and food taken with telaprevir should be ingested no more than 30 minutes prior to each dose. The recommended dose of boceprevir is 800 mg (four 200-mg capsules) three times daily (7-9 hours apart) with food.[4] The product labeling does not specify fat content of food to be taken with boceprevir. Dose adjustments for renal impairment are generally not necessary for either medication since the main routes of metabolism and elimination are hepatic.[1,4,5] Dosage adjustments are not required for boceprevir in the setting of cirrhosis and liver impairment with the exception of decompensated cirrhosis, where its use has not been studied and is not recommended. However, telaprevir has not been adequately studied in patients with moderate-to-severe hepatic impairment and should not be used in this setting. Telaprevir may be used in patients with mild hepatic impairment without dosage adjustment. Furthermore, neither boceprevir nor telaprevir have been studied in the pediatric population; therefore, their use in pediatric patients is not recommended. Duration of therapy with boceprevir or telaprevir is based on specific patient populations and when certain viral load levels are detected.[4,5] The specific patient populations include previously untreated patients, null responders defined as patients whose HCV RNA level did not decline by at least 2 log IU/mL at treatment week 12 of prior standard therapy with peginterferon alfa and ribavirin, partial responders whose HCV RNA level dropped by at least 2 log IU/mL at treatment week 12 but in whom HCV RNA was still detected at treatment week 24, and relapsers whose HCV RNA became undetectable during prior treatment, but then reappeared after treatment ended.[1] Guidelines which outline treatment duration are summarized in Tables 1 and 2.

Product Labeling Changes: Since their introduction into the market, there have been important changes noted in the product labeling of each medication. In clinical use, serious acute hypersensitivity reactions (e.g., SJS, DRESS, and TEN) have been seen in patients taking boceprevir, peginterferon alfa, and ribavirin.[6] The product labeling lists prior hypersensitivity reactions to this combination therapy as a contraindication. Additionally, stronger, black boxed warnings have been added to the labeling for telaprevir regarding fatal and non-fatal serious skin reactions including SJS, DRESS, and TEN.

Formulary Restrictions: Boceprevir and telaprevir are restricted to the Departments of Hepatology, Transplant Services, and Infectious Diseases for continuation of therapy from home in adult patients.

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Table 1: Guidelines for Duration of Therapy with Boceprevir, Peginterferon Alfa, and Ribavirin in Patients Without Cirrhosis [4]

	Assessment HCV-RNA Results		Recommendation*
	At TW8	**At TW24**	
Previously Untreated Patients	Not Detected	Not Detected	1. Continue three-medicine regimen through TW28
Previously Untreated Patients	Detected	Not Detected	1. Continue three-medicine regimen and finish through TW36; and then 2. Administer peginterferon alfa and and ribavirin and finish through TW48
Previous Partial Responders or Relapsers	Not Detected	Not Detected	1. Continue three-medicine regimen through TW36
Previous Partial Responders or Relapsers	Detected	Not Detected	1. Continue three-medicine and finish through TW36; and then 2. Administer peginterferon alfa and ribavirin and finish through TW48
Previous Null Responders	Detected or Not Detected	Not Detected	1. Continue three-medicine regimen through TW48

HCV RNA=hepatitis C virus ribonucleic acid TW=treatment week
*If HCV RNA results ≥ 100 IU/mL at TW12, discontinue three-medicine regimen
If HCV RNA is detectable at TW24, discontinue three-medicine regimen

Table 2: Guidelines for Duration of Therapy with Telaprevir, Peginterferon Alfa, and Ribavirin[5]

	Assessment HCV-RNA Results		Recommendation*
	At TW4	**At TW12**	
Previously Untreated Patients and Prior Relapse Patients	Not Detected	Not Detected	1. Complete three-medicine regimen for 12 weeks then 2. Administer peginterferon alfa and ribavirin and finish through TW24
Previously Untreated Patients and Prior Relapse Patients	Detected	Detected	1. Continue three-medicine regimen for 12 weeks and finish through TW12; and then 2. Administer peginterferon alfa and ribavirin and finish through TW48
Previous Partial Responders or Null Responders (All Patients)	N/A	N/A	1. Continue three-medicine regimen for 12 weeks and finish through TW12; and then 2. Administer peginterferon alfa and ribavirin and finish through TW48

HCV RNA=hepatitis C virus ribonucleic acid N/A= not applicable TW=treatment week
*If HCV RNA results >1000 IU/mL at TW4 or TW12 or confirmed detectable HCV RNA levels at TW24, discontinue three-medicine regimen at TW12
If HCV RNA is detectable at TW24, discontinue peginterferon alfa and ribavirin

Formulary Update

Additions to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Buprenorphine (Subutex®)	Opioid Partial Agonist	Management of Opioid Dependence	Prescribing is limited to physicians with specific DEA number and DATA 2000 waiver Exceptions: 1) Prescribing for off-label use (e.g., pain control) 2) Use in patients admitted for a primary medical problem other than opioid addiction to prevent opioid withdrawal
Hemin for Injection (Panhematin®)	Blood Modifier	Recurrent attacks of acute intermittent porphyria	Restricted to Hematology/ Oncology
Hyaluronidase-recombinant (Hylenex®)	Enzyme	Adjunct to periocular blocks to help prevent eye muscle toxicity	Restricted to Ophthalmology for outpatient use only

DEA=Drug Enforcement Agency

Addition to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Permethrin 1% Lotion (Nix®)	Antiparasitic Agent	Treatment of lice infestation	First-line agent endorsed by American Academy of Pediatrics and the CDC Lindane 1% Shampoo is no longer recommended as first-line therapy for the treatment of lice and therefore removed from the Pediatric Formulary

CDC=Centers for Disease Control and Prevention

Restriction Changes to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Bortezomib (Velcade®)	Proteasome Inhibitor Antineoplastic Agent	Cancer Treatment of antibody mediated rejection	Original restrictions: Hematology/Medical Oncology Treatment of antibody mediated rejection in kidney transplant recipients Additional restriction: Desensitization protocols for heart and intestinal transplants
Cetuximab (Erbitux®)	Antineoplastic Agent	Cancer (e.g., colorectal, head and neck)	Original restriction: The Department of Hematology/ Medical Oncology New restriction: The Department of Hematology/Medical Oncology for outpatients only
Clofarabine (Clolar®)	Antineoplastic Agent	Acute lymphoblastic leukemia (ALL) Acute myelocystic leukemia (AML)	Original restriction: Clofarabine use is restricted to pediatric patients 1-21 years of age with relapsed or refractory acute lymphoblastic leukemia. New restriction; The Department of Hematology/Oncology
Pegaspargase (Oncaspar®)	Antineoplastic Agent	Kaposi's sarcoma and other malignancies	Original restriction: Restricted to patients who are hypersensitive to L-asparaginase or pediatric patients New restriction: Restricted to Hematology/Oncology
Prothrombin Complex Concentrate Factor IX (Profilnine®SD)	Hemostatic Agent	Warfarin reversal	Restriction Changes: The Department of Neurology and Neurosurgery, Emergency Room physicians, and Intensivists for warfarin-related life-threatening intracranial hemorrhage for patients with heparin-allergy or HIT who cannot receive Kcentra® The reversal of warfarin prior to heart transplant
Triamcinolone acetonide (Triesence®)	Corticosteroid	Treatment of ocular inflammatory conditions	Restricted to Ophthalmology for outpatient use only

HIT=Heparin-induced thrombocytopenia

Restriction Changes to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Clobazam (Onfi®)	Benzodiazepine	Lennox-Gastaut Syndrome	Original restriction: Continuation of home therapy for pediatric patients. Current restriction: Expanded to include initiation of therapy in patients with Lennox-Gastaut Syndrome who have failed other therapies.
Codeine	Opioid Analgesic	Pain Management	Codeine use in pediatric patients is restricted. Codeine and codeine-containing medications should NOT be prescribed for postoperative pain management in pediatric patients (i.e., < 18 years of age) undergoing tonsillectomy and/or adenoidectomy. Alternative pain therapies must be selected for these patients.
Injectable bumetanide (Bumex®)	Loop Diuretic	Edema	Restriction modified to include patients in the Neonatal Intensive Care Unit who do not respond to furosemide therapy
Intravenous Acetaminophen (Ofirmev™)	Analgesic	Pain Management	Restriction modified to state that IV acetaminophen can be prescribed in all Intensive Care Units within the Children's Hospital for pediatric patients 40 weeks post-conceptual and older All other IV acetaminophen restrictions must still be followed
Palifermin (Kepivance®)	Keratinocyte Growth Factor Protectant	Severe Mucositis	Restriction modified to include patients with germ cell tumors receiving tandem chemotherapy regimen TIC/TEC

TEC=paclitaxel, etoposide, carboplatin TIC=paclitaxel, ifosfamide, carboplatin