Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Washington Pharmacy Advisory Committee Meeting

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Agenda Topics

- Overview of Disease State
- Indications
- Dosage & Formulations
- Guideline Updates

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Antibiotics:
- Aminoglycosides- Inhaled
- Monobactams- Inhaled

Respiratory Agents:
- Cystic Fibrosis Agents

Disease State Description - Cystic Fibrosis

- Cystic Fibrosis (CF) is a serious autosomal recessive multiorgan disorder
- Affects ~30,775 children and adults in the U.S. and is the most common fatal genetic disease in Caucasians
  - The median survival in patients with CF is 47.4 years with 80% of patients reaching adulthood
  - Children are anticipated to live to approximately 40 years of age with current treatments
  - In 2018, adults comprised approximately 54.6% of the CF population, while in 1988, they comprised approximately 31.1%
- Mutations lead to the disease of the exocrine gland function, resulting in the formation of thick mucus that builds up in the lungs, digestive tract, and other parts of the body
  - CF transmembrane conductance regulator (CFTR) functions as a chloride channel
  - Mutations in CFTR results in abnormalities of chloride transport across epithelial cells on mucosal surfaces
- Goals of CF treatment include:
  - Maintaining lung function by controlling infection and clearing mucus in the airway
  - Maintaining appropriate growth by providing nutritional support (e.g., enzyme, mineral, and multivitamin supplements)
  - Managing disease complications (e.g., insulin therapy in patients who develop diabetes)

Cystic Fibrosis Foundation, 2018

Guidelines - Cystic Fibrosis

- Goals of CF treatment include maintaining lung function by controlling infection and clearing mucus in the airway, maintaining appropriate growth by providing nutritional support (e.g., enzyme, mineral, and multivitamin supplements) and managing disease complications (e.g., insulin therapy in patients who develop diabetes)
- *CFTR* modulators (potentiators or correctors) are the newest class of medications available for this disease and improve chloride ion transport abnormalities

- Cystic Fibrosis Foundation, 2013
  - Inhaled treatments (e.g., tobramycin, dornase alfa, hypertonic saline, corticosteroids) and oral treatments (e.g., antibiotics, corticosteroids) for treatment of symptoms, exacerbations, and/or infections
  - Chronic treatment of ivacaftor for individuals 6 years of age and older with at lease one *G551d CFTR* mutation to improve lung function and quality of life and to reduce exacerbations

- Clinical Pharmacogenetics Implementation Consortium (CPIC), 2014
  - Recommend ivacaftor therapy based on *CFTR* genotype in CF patients ≥ 6 years old who are homozygous or heterozygous for the *G551D CFTR* variant
  - CPIC further states that there are no data regarding whether or not ivacaftor can replace other established therapy

- Please note: Orkambi, Symdeko, and Trikafta were not approved in 2013/2014 and were not addressed in either guideline

Updated Information - Cystic Fibrosis

- ivacaftor (Kalydeco)
  - **In August 2020, FDA expanded indication for the treatment of cystic fibrosis (CF) in patients age 4 to < 6 months of age and weighing ≥ 5 kg who have ≥ 1 mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data; previously, it was only approved in patients ≥ 6 months of age**
  - **Indication**
    - **Treatment of cystic fibrosis (CF) in patients age 4 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data**
  - **Dosage**
    - Adults and children ≥ 6 years of age: one 150 mg tablet orally every 12 hours (300 mg/day)
    - **Pediatric patients 4 months to < 6 months of age and < 5 kg: one 25 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food**
    - **Pediatric patients 6 months to < 6 yo and weighing 5 kg to < 7 kg: one 25 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food**
    - **Pediatric patients 6 months to < 6 yo and weighing 7 kg to < 14 kg: one 50 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food**
    - **Pediatric patients 6 months to < 6 yo and > 14 kg: one 75 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food**
  - **Availability**
    - 150 mg tablets
    - 25 mg, 50 mg, 75 mg oral granules in unit-dose packets

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Anticoagulants:
- Factor Xa and Thrombin Inhibitors - Oral

Disease State Description - Anticoagulants

Venous Thromboembolism (VTE)

- It manifests as deep vein thrombosis (DVT) and pulmonary embolism (PE) and is a major consequence of various surgical procedures and medical conditions
- DVT occurs when a thrombus composed of cellular material bound together with fibrin strands forms in the deep venous portion of the extremities, most commonly the legs
  - The exact number of patients impacted by DVT and PE is unknown; however, it is estimated these conditions affect between 300,000 and 600,000 people in the U.S. every year
  - If left untreated, approximately 30% of patients who develop PE will die within the first few hours of the event
- Generally, the risk of VTE increases with the number of risk factors present, major traumas, and age
- Due to the risk of morbidity and fatal PE associated with DVT, prophylaxis has become the standard of care for patients at high risk for thrombosis

National Heart, Lung, and Blood Institute, 2017

CAD (Coronary Artery Disease) and Peripheral Artery Disease (PAD)

- Approximately 14 million Americans have CAD, and 8.5 million over the age of 40 years have PAD
- Prevention and treatment of atherosclerosis focus on modifiable risk factors
- Therapy includes lifestyle changes and the medical treatment of hypertension, hyperlipidemia, and diabetes mellitus
- Antiplatelet medications (e.g., aspirin, clopidogrel, prasugrel, ticagrelor, vorapaxar) are indicated for reduction of thrombotic CV events in patients with established CAD or PAD

American College of Cardiology, 2016

Disease State Description - Anticoagulants

Atrial Fibrillation (AF)

- A common arrhythmia ranging in prevalence from 2% in patients under 65 years of age to 9% for those 65 or older
  - The prevalence is higher in men than in women and increases with age
  - More than a third of patients with AF are 80 years of age or older

- Patients with AF can have a reduction in cardiac output resulting in pooling of blood in the heart, atrial thrombus formation, and potential systemic embolization
  - Ischemic stroke is the most frequent clinical manifestation of AF associated embolization
  - AF increases the risk of stroke 5-fold

- In patients with AF, ACCP recommends measuring thromboembolism risk using the CHA_2DS_2-VASc score, which considered risk factors such as gender, age, history of stroke, TIA, or thromboembolism, as well as history of congestive heart failure (CHF), hypertension, diabetes mellitus, or vascular disease (prior myocardial infarction [MI], peripheral artery disease, or aortic plaque)
  - The score ranges from 0 to 9, with higher numbers indicating more risk

American College of Cardiology, 2017

Treatment Guidelines - Anticoagulants

American Heart Association/American College of Cardiology (AHA/ACC), 2020

- Published guidelines on the diagnosis and treatment of hypertrophic cardiomyopathy (HCM)
- Notable pharmacologic recommendations include the following:
  - For symptomatic patients with left ventricular outflow tract (LVOT) obstruction, nonvasodilating beta-blockers are recommended, but alternatives for select patients include verapamil, diltiazem, or disopyramide
  - For non-obstructive hypertrophic cardiomyopathy with preserved left ventricular ejection fraction (LVEF), beta-blockers, verapamil, or diltiazem are recommended and consideration of anticoagulants as the default treatment option for patients who also have atrial fibrillation independent of the CHA2DS2VASc score
  - Additional guidance on the use of antiarrhythmic therapy and heart failure agents is included as well

American College of Cardiology (ACC), 2020

- Published an expert consensus decision pathway on managing bleeding episodes in patients taking oral anticoagulants
- It updates parts of the 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation
- Provides guidance for temporary or permanent interruption of therapy, general approaches to bleeding management, decision support for treatment with a reversal agent, and indications and timing for reinstituting anticoagulant treatment
- The panel does not recommend routine administration of platelets for patients on antiplatelet agents for major bleeding
- They do not recommend routine oral anticoagulant reversal for nonmajor bleeding, but clinicians may interrupt therapy until patient is clinically stable and hemostasis is achieved

Updated Information - Anticoagulants

- Discontinuation
  - **betrixaban (Bevyxxa), May 2020**
    - **The FDA is reporting Portola Pharmaceuticals will be discontinuing Bevyxxa (betrixaban) capsules in the strengths of 40 mg and 80 mg**

- New Generic
  - **Apixaban, January 2020**
    - **FDA approved first generics for Eliquis from Mylan and Micro Labs**

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Antidiabetics:
- Amylin Analogs
- SGLT2 Inhibitors
- DPP4 Inhibitor
- DPP4 Inhibitor/ SGLT2 Inhibitor Combinations
- DPP4 Inhibitor/ TZD Combinations
- GLP1 Agonists
- GLP1 Agonist/ Insulin Combinations

Disease State Description - Diabetes Mellitus

- It is estimated that over 34 million Americans have diabetes mellitus (DM)
  - Of which, 90-95% have Type 2 Diabetes
  - Diabetes is responsible for increased morbidity and mortality
- Adequate glycemic control is crucial to minimize chronic microvascular (e.g., blindness, renal dysfunction) and macrovascular (e.g., cardiovascular disease [CVD]) complications
- Exogenous insulin supplements deficient levels of endogenous insulin, and temporarily restores the ability of the body to properly utilize carbohydrates, fats, and proteins
- Multiple insulin products are available and are used as replacement therapy in the management of both T1DM and T2DM when glycemic goals are not met with oral antidiabetic agents
- In addition to exogenous insulin, there are several pathways by which blood glucose may be regulated in diabetic patients
- The sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce renal glucose reabsorption in the proximal convoluted tubule, leading to increased urinary glucose excretion

American Diabetes Association, 2020

Guidelines- Diabetes Mellitus

- Endocrine Society, 2019
  - Released recommendations for diabetes in patients aged ≥ 65 years
  - Recommend simplified outpatient medication regimens and glycemic targets tailored to improve compliance and prevent complications, such as hypoglycemia and falls, particularly in patients with cognitive impairment
    - First-line treatment for ambulatory patients is lifestyle modification
    - When pharmacological therapy is indicated, metformin, in addition to lifestyle management, is recommended first-line
    - If glycemic targets are not attained with metformin and lifestyle management, oral and injectable therapies with low risk for hypoglycemia are suggested
    - The guidelines also have recommendations for management of common comorbidities in this population including hypertension, hyperlipidemia, congestive heart failure, retinopathy, neuropathy, and chronic kidney disease
    - Additionally, SGLT2 inhibitors have been shown to reduce major adverse cardiovascular events (MACE), heart failure, and progression of CKD
      - Consequently, these should be prescribed early in treatment
        - Due to adverse effects related to volume depletion with canagliflozin, dosages should be limited to 100 mg/day in susceptible patients (e.g. elderly)

Guidelines- Diabetes Mellitus

- American College of Cardiology, 2020
  - The ACC published an expert consensus decision pathway for CV risk reduction in patients with T2DM
  - They identify opportunities to initiate an SGLT2 inhibitor or GLP-1RA with demonstrated CV or renal benefit in patients with T2DM
    - A medication from either class may be initiated in any patient with T2DM and ASCVD at the time of diagnosis of T2DM or ASCVD or any time after diagnosis, including at hospital discharge for ASCVD
    - An agent from either class can also be started in patients with T2DM without established ASCVD but who are at high risk of ASCVD
  - In addition, initiation of an SGLT2 inhibitor with demonstrated CV or renal benefit is recommended in patients with Heart Failure and/or diabetic kidney disease
  - A GLP-1RA is an alternative in patients with eGFR < 30 ml/min/1.73 m^2

- Kidney Disease: Improving Global Outcomes (KDIGO), 2020
  - Published its first guidelines on managing diabetes in patients with chronic kidney disease (CKD)
  - Key recommendations include:
    - Patients with diabetes, hypertension, and albuminuria should start treatment with an ACEI or ARB
    - Monitor glycemic control using HbA1c in patients with diabetes and CKD
      - Target HbA1c range from < 6.5% to < 8% in those not on dialysis depending on hypoglycemia risk
    - Metformin and a SGLT2 inhibitor are recommended in patients with eGFR ≥ 30 mL/min/1.7 m2
      - If glycemic targets are not met, then a long-acting GLP-1 agonist is recommended

Guidelines- Diabetes Mellitus

- American Diabetes Association (ADA), 2020
  - ADA updated select sections of their living Standards of Medical Care in Diabetes – 2020
  - For diabetes technology, an automated insulin delivery system should be considered in adults with T1DM who have the skills to use the device in order to improve time in range and reduce A1C and hypoglycemia (A-rated recommendation)
    - These systems may also be useful to improve glycemia in children (B-rated recommendation)
  - Regarding obesity management, ADA states that lorcaserin should no longer be used, as the FDA requested its market withdrawal
  - For pharmacologic T2DM therapy, ADA advises to interrupt SGLT2 inhibitor therapy before scheduled surgery to avoid diabetic ketoacidosis, this aligns with label revisions for SGLT2 inhibitors
  - For management of CVD in patients with T2DM, ADA advises to consider an SGLT2 inhibitor in patients with Heart Failure (HF) with reduced ejection fraction to reduce risk of worsening HF and CV death

Updated Information - Hypoglycemics, SGLT2 Inhibitors

- canagliflozin/metformin (Invokamet; Invokamet XR)
  - **January 2020: FDA approved new indication to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with T2DM and diabetic nephropathy with albuminuria > 300 mg/day. Previously, this was approved only to reduce the risk of MACE and as an adjunct to diet and exercise to improve glycemic control in T2DM**
  - **August 2020: FDA issued Drug Safety Communication to update an earlier communication regarding the risk of leg and foot amputations with canagliflozin-containing medications. The update states that, based on review of data from 3 new clinical trials, they have removed the Boxed Warning language from PIs of canagliflozin-containing medications. The risk of amputation remains a warning in the labeling**
  - **Indications**
    - As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
    - Canagliflozin is indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease
    - **Canagliflozin is indicated to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria**
    - Limitations of Use: Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis
  - **Dosing**
    - Individualize starting dose based on the patient's current regimen and renal function
    - Invokamet: Recommended starting dose of canagliflozin is 50 mg twice daily and metformin HCl 500 mg twice daily
    - Invokamet XR: Once daily with the morning meal
    - Gradually escalate metformin HCl dose to reduce the gastrointestinal side effects while not exceeding a total daily dose of 2,000 mg
  - **Precautions**
    - BBW: Lactic Acidosis
    - BBW: Risk of Lower Limb Amputation
  - **Formulations**
    - Invokamet and Invokamet XR tablets: Canagliflozin 50, 150 mg and metformin HCl 500, 1000 mg combinations

Updated Information - Hypoglycemics, SGLT2 Inhibitors

- dapagliflozin (Farxiga)
  - **May 2020: FDA approved new indication to reduce the risk of CV death and hospitalization for heart failure (HF) in adults with HF with reduced ejection fraction (NYHA class II-IV)**
  - **Indications**
    - Type 2 Diabetes Mellitus:
      - As an adjunct to diet and exercise to improve glycemic control
      - To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors
    - **Heart Failure:**
      - **To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV)**
    - Limitations of use: Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis
  - **Dosing**
    - Type 2 Diabetes Mellitus: Recommended starting dose is 5 mg once daily (Max: 10 mg daily)
    - **Heart Failure: 10 mg once daily**
  - **Precautions**
    - Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters
    - Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Serious, life-threatening cases have occurred in patients with diabetes, both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise
    - Volume depletion: Before initiating, assess volume status and renal function in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics
  - **Formulations**
    - **Tablets: 5 and 10 mg**

Updated Information - Hypoglycemics, SGLT2 Inhibitors

- empagliflozin/linagliptin/ metformin (Trijardy XR)
  - **January 2020: FDA approved Trijardy XR, a combination of empagliflozin (SGLT2 inhibitor), linagliptin (DPP-4 inhibitor), and metformin (a biguanide), as an adjunct to diet and exercise to improve glycemic control in adults with T2DM**
  - **Indications**
    - **An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus**
    - **Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease**
    - **<u>Limitations of Use</u>:**
      - **Not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis**
      - **Has not been studied in patients with a history of pancreatitis**
  - **Precautions**
    - **BBW: Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2**
    - **Lactic Acidosis**
  - **Dosing**
    - **Individualize the starting dose based on the patient's current regimen; maximum recommended dose is 25/5/2000 mg**
    - **Do not initiate or continue if eGFR is < 45 mL/min/1.73 m^2**
  - **Formulations**
    - **Tablets:**
      - **5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin HCl extended-release**
      - **10 mg empagliflozin/5 mg linagliptin/1000 mg metformin HCl extended-release**
      - **12.5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin HCl extended-release**
      - **25 mg empagliflozin/5 mg linagliptin/1000 mg metformin HCl extended-release**

Updated Information - Hypoglycemics, Glucagon-like-Peptide 1 (GLP-1)

- semaglutide (Ozempic)
  - **December 2019: FDA approved a new formulation of a new pen injector that incorporates a 3 mL cartridge and is designed to deliver 4 doses of 1 mg semaglutide approved**
  - **January 2020: FDA approved a new indication to reduce the risk of major adverse CV events (CV death, non-fatal MI or non-fatal stroke) in adults with DM and established CV disease**
  - **Indications**
    - An adjunct to diet and exercise to improve glycemic control in adults with type 2 DM
    - **To reduce the risk of major adverse cardiovascular events in adults with type 2 DM and established cardiovascular disease**
  - **Dosing**
    - Start at 0.25 mg once weekly
      - After 4 weeks, increase the dose to 0.5 mg once weekly. If after at least 4 weeks additional glycemic control is needed, increase to 1 mg once weekly
  - **Precautions/Contraindications**
    - BBW: In rodents, semaglutide causes thyroid C-cell tumors. It is unknown whether Rybelsus causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined
    - BBW: Contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
  - **Formulations**
    - Injection: 2 mg/1.5 mL (1.34 mg/mL) available in:
      - Single-patient-use pen that delivers 0.25 mg or 0.5 mg per injection
      - **Single-patient-use pen that delivers 1 mg per injection**

Updated Information - Hypoglycemics, Glucagon-like-Peptide 1 (GLP-1)

- dulaglutide (Trulicity)
  - **February 2020: FDA approved for new indication of reduction in the risk of major adverse cardiovascular events (MACE) (CV death, non-fatal MI, or non-fatal stroke) in adults with T2DM who have established CV disease or multiple CV risk factors**
  - **Indications**
    - As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
    - **To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors**
    - Limitations of Use: Has not been studied in patients with a history of pancreatitis; not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis; not for patients with pre-existing severe gastrointestinal disease
  - **Dosing**
    - Start at 0.75 mg once weekly; dose can be increased to 1.5 mg once weekly for additional glycemic control
  - **Precautions/Contraindications**
    - BBW: In rodents, causes thyroid C-cell tumors. It is unknown whether Rybelsus causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined
    - BBW: Contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
  - **Formulations**
    - Injection: 0.75 mg/0.5 mL solution in a single-dose pen
    - Injection: 1.5 mg/0.5 mL solution in a single-dose pen

Updated Information - Hypoglycemics, Glucagon-like-Peptide 1 (GLP-1)

- **liraglutide (Saxenda)**
  - December 2020: FDA approved Saxenda for pediatric patients ≥ 12 y/o who are ≥ 60 kg and have an initial BMI corresponding to 30 kg/m^2 for adults (obese) by international cutoffs; previously, it was approved only in adults
  - Indications
    - An adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in:
      - Adult patients with an initial body mass index (BMI) of
        - 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g. hypertension, type 2 diabetes mellitus, or dyslipidemia)
      - Pediatric patients aged 12 years and older with body weight above 60 kg and an initial BMI corresponding to 30 kg/m2 for adults (obese) by international cut-offs
  - Dosing
    - Inject subcutaneously in the abdomen, thigh, or upper arm once daily at any time of day, without regard to the timing of meals
    - Initiate at 0.6 mg per day for one week; in weekly intervals, increase the dose until a dose of 3 mg is reached
  - Precautions/Contraindications
    - BBW: In rodents, causes thyroid C-cell tumors. It is unknown whether Saxenda causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined
    - BBW: Contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
    - Contraindicated in patients who are pregnant as it may result in fetal harm
  - Formulations
    - Injection: 6 mg/mL solution in a 3 mL pre-filled, single-patient-use pen that delivers doses of 0.6, 1.2, 1.8, 2.4, or 3 mg

Hypoglycemics, DPP4 Inhibitors

- **FDA Communication**
  - FDA issued communication stating that sitagliptin (Januvia), sitagliptin/metformin (Janumet), and sitagliptin/metformin ER (Janumet XR) are not proven to improve glycemic control in patients 10 to 17 y/o with T2DM
  - This is based on results of 3 clinical trials that did not demonstrate an improvement in HbA1c. Labeling has been updated accordingly

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Antidiabetics: Insulin

Updated Information – Rapid-Acting Insulin

- **FDA Announcement**
  - **December 2019: FDA has published a statement regarding the pathway for approval of "chemically synthesized polypeptides." In March 2020, the majority of protein products (including all current insulin products) will have the potential for biosimilar and interchangeable products to increase competition through FDA approval under abbreviated pathways. However, products that are deemed "chemically synthesized polypeptides" are not eligible for the abbreviated approval pathways utilized for biosimilar or interchangeable products. The statement addresses how removal of this exclusion would allow for chemically synthesized follow-on insulins and other products to become approved through abbreviated pathways as well**
  - **March 2020: As part of Biosimilars Action Plan, FDA announced that insulin and certain other biologic products have transitioned to a different regulatory pathway as of March 23, 2020**
  - **October 2020: FDA issued a communication to clarify the intent of the November 2019 revisions to labeling for insulin pens, which state that Healthcare Practitioners should dispense the pens to a single patient in the original sealed carton. Insulin pens are not labeled for dispensing as individual units. Because sealed cartons of insulin pens are intended to be dispensed to a single patient, each carton contains a single copy of the drug's PI and instructions for use. FDA has strongly encouraged insulin pen manufacturers to consider developing smaller carton sizes to better accommodate variable insulin doses. FDA suggests organizations facing challenges with multiple-pen cartons contact the manufacturers to express the need for smaller (and single-pen) carton sizes**

- **insulin lispro (Insulin Lispro KwikPen)**
  - **April 2020: Lilly announced launch of new authorized generic for Humalog Junior KwikPen (insulin lispro injection, 100 units/mL)**

Updated Information – Rapid-Acting Insulin

- **insulin aspart injection (Fiasp)**
  - **January 2020: FDA expanded the approval for improving glycemic control in patients with diabetes mellitus to include pediatric patients, including for the use as continuous SC insulin infusion; previously it was approved in adults only**
  - **Indications**
    - **A rapid-acting human insulin analog indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus**
  - **Dosing**
    - Individualize dosage based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, prior insulin use
  - **Precautions/Contraindications**
    - Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated
    - Never share prefilled pen between patients, even if the needle is changed
    - Contraindications:
      - During episodes of hypoglycemia
      - Hypersensitivity to one of its excipients
  - **Formulations**
    - Injection: 100 units/mL is available as:
      - 10 mL multiple-dose vial
      - 3 mL single-patient-use prefilled pen
      - 3 mL single-patient-use cartridges for use in cartridge device

Updated Information – Rapid-Acting Insulin

- **insulin lispro-aabc (Lyumjev)**
  - **June 2020: FDA approved Lyumjev, a rapid-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus**
  - **Indications**
    - **A rapid-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus**
  - **Dosing**
    - **Individualize dosage based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, prior insulin use**
    - **Subcutaneous Injection: Administer at the start of a meal or within 20 minutes after starting a meal subcutaneously into the abdomen, upper arm, thigh, or buttocks**
    - **Intravenous Infusion: Administer intravenously only under medical supervision**
  - **Precautions/Contraindications**
    - **Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated**
    - **Never share prefilled pen between patients, even if the needle is changed**
    - **Contraindications:**
      - **During episodes of hypoglycemia**
      - **Hypersensitivity to one of its excipients**
  - **Formulations**
    - **Injection: 100 units/mL is available as: 10 mL multiple-dose vial, 3 mL single-patient-use KwikPen, 3 mL single-patient-use Junior KwikPen, 3 mL single-patient-use Tempo Pen, 3 mL single-patient-use cartridges**
    - **Injection: 200 units/mL (U-200) available as: 3 mL single-patient-use KwikPen**

Updated Information – Rapid/Intermediate-Acting Combination Insulin

- insulin lispro protamine/insulin lispro (Insulin Lispro Protamine/Insulin Lispro KwikPen)
  - **April 2020:** Lilly announced launch of new authorized generic for Humalog Mix75/25 KwikPen (insulin lispro protamine and insulin lispro injectable suspension, 100 units/mL)

Updated Information – Long-Acting Insulin

- **insulin glargine (Basaglar)**
  - **December 2019: FDA approved the expanded formulation of the addition of a modified pre-filled insulin pen that can be used with connected devices, mobile applications, or other technology (3 mL single-patient-use Basaglar Tempo Pen)**
  - **Indications**
    - Improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus
    - Limitations of Use: Not recommended for treating diabetic ketoacidosis
  - **Dosing**
    - Individualize dosage based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, prior insulin use
  - **Precautions/Contraindications**
    - Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated
    - Never share prefilled pen between patients, even if the needle is changed
    - Contraindications:
      - During episodes of hypoglycemia
      - Hypersensitivity to one of its excipients
  - **Formulations**
    - Injection: 100 units/mL (U-100) is available as:
      - 3 mL single-patient-use KwikPen
      - **3 mL single-patient-use Tempo Pen**

Updated Information – Long-Acting Insulin

- **insulin glargine (Toujeo Solostar, Toujeo Max Solostar)**
  - **December 2019: FDA expanded indication to include pediatrics 6 to 17 years old with diabetes mellitus**
  - **Indications**
    - To improve glycemic control in **adults and pediatric patients 6 years and older** with diabetes mellitus
    - Limitations of Use: Not recommended for treating diabetic ketoacidosis
  - **Dosing**
    - Individualize dosage based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, prior insulin use
  - **Precautions/Contraindications**
    - Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated
    - Never share prefilled pen between patients, even if the needle is changed
    - Contraindications:
      - During episodes of hypoglycemia
      - Hypersensitivity to one of its excipients
  - **Formulations**
    - Injection: 300 units/mL is available as:
      - 1.5 mL SoloStar single-patient-use prefilled pen
      - 3 mL Max SoloStar single-patient-use prefilled pen

Updated Information – Long-Acting Insulin

- **insulin glargine (Semglee)**
  - **June 2020: FDA approved Semglee under the 505(b)(2) NDA pathway and is now deemed a biologic. It is a long-acting human insulin analog, indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with T2DM**
  - **Indications**
    - **To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus**
    - **Limitations of Use: Not recommended for treating diabetic ketoacidosis**
  - **Dosing**
    - **Individualize dosage based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, prior insulin use**
  - **Precautions/Contraindications**
    - **Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated**
    - **Never share prefilled pen between patients, even if the needle is changed**
    - **Contraindications:**
      - **During episodes of hypoglycemia**
      - **Hypersensitivity to one of its excipients**
  - **Formulations**
    - **Injection: 100 units/mL (U-100) is available as:**
      - **10 mL multiple-dose vial**
      - **3 mL single-patient-use prefilled pen**

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Endocrine and Metabolic Agents: Growth Hormone Releasing Hormones (GHRH)

Overview of Disease State – Growth Factors

- Growth hormone insensitivity or insulin-like growth factor-1 (IGF-1) deficiency refers to a variety of disorders characterized by the resistance to growth hormone
  - Growth hormone insensitivity can be defined by a deficiency in the production of growth hormone or peripheral action of IGF-1 on linear growth
  - Severe primary IGF-1 deficiency is due to a mutation of the growth hormone receptor or post-growth hormone receptor signaling
  - Severe primary IGF-1 deficiency is also characterized by the development of growth hormone inactivating antibodies in pediatric patients with growth hormone gene deletion
    - Patients are considered to have severe primary IGF-1 deficiency when the following criteria are met: height standard deviation score ≤ -3, basal IGF-1 standard deviation score ≤ -3, and normal or elevated growth hormone

- HIV Lipodystrophy
  - Soon after combination antiretroviral therapy was found effective in treating HIV infected patients, adverse side effects from the medications were reported, including metabolic changes, morphological abnormalities and lipodystrophy
  - HIV lipodystrophy is found in patients on highly active anti-retroviral therapy (HAART)
  - Patients with HIV lipodystrophy were described as having a loss of subcutaneous fat in limbs, face, and buttocks and an accumulation of fat in other areas of the body including the abdominal viscera
  - Patients who have increased visceral abdominal fat and waist circumference are at an increased risk for metabolic syndrome, cardiovascular disease, atherosclerosis, and diabetes mellitus

Guidelines - Growth Factors

- Severe IGF-1 Deficiency/Growth Hormone Gene Deletion
  - Increlex is the only available product approved for the indication of long-term treatment of growth failure in pediatric patients with severe primary IGF-1 deficiency or with growth hormone gene deletion with development of neutralizing antibodies to growth hormone
  - Patients with diagnoses that are not growth hormone deficient and will not respond well to exogenous growth hormone
  - Likewise, mecasermin (Increlex) should not be used as a substitute for patients who require growth hormone therapy
  - Increlex should not be used in patients with secondary forms of IGF-1 deficiency and all thyroid and nutritional issues should be corrected prior to initiating Increlex therapy
  - Increlex should not be used for weight loss management

- HIV Lipodystrophy
  - Recombinant human growth hormone (rhGH) has been used with success in patients with AIDS-related wasting syndrome since it has been shown to improve muscle mass
  - However, studies have shown rhGH causes a reduction in visceral adiposity but supra-physiologic levels of IGF-1 and symptoms of excess growth hormone occurred causing treatment cessation
  - Egrifta offers a specific treatment option for the reduction of excessive abdominal fat in HIV patients with lipodystrophy as it appears to target the visceral fat compartment with little effect on subcutaneous fat or fat in the limbs

Updated Information - Growth Factors

- Discontinuation:
  - **tesamorelin for injection (Egrifta), May 2020**
    - Brand-name product Egrifta is being discontinued by the manufacturer (Theratechnologies) and is being replaced with the new smaller volume (SV) formulation Egrifta SV which became available in December 2019 and can be stored at room temperature
    - Egrifta is not available as of June 15, 2020

Magellan Rx MANAGEMENT℠

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Endocrine and Metabolic Agents: Growth Hormone

Overview of Disease State & Guidelines – Growth Hormones

- **Human growth hormone (hGH, somatropin)**
  - A 191-amino acid polypeptide hormone secreted by the anterior pituitary gland
  - It has important metabolic effects, including stimulation of protein synthesis and cellular uptake of amino acids
  - Short stature and growth deceleration are common pediatric concerns, and exogenous growth hormone is used to treat a variety of disorders in which endogenous growth hormone is insufficient to meet the needs of the patient

- **Growth hormone deficiency (GHD)**
  - Results from inadequate production of growth hormone (GH) and can produce various medical conditions dependent on age
  - GHD can be congenital or acquired in childhood or adult life, in addition to being partial or complete. In infancy and childhood, growth failure may be the major effect
  - Adults with GHD may have diminished lean body mass, poor bone density, and a number of physical and psychological manifestations
  - GHD is usually permanent and may be an isolated deficiency or occur in association with deficiencies of other pituitary hormones
  - Between 40% to 50% of childhood cancer survivors develop an endocrine disorder during their lifetime, with some developing decades following cancer treatment

- **AACE Growth Hormone Task Force, 2019**
  - Does not advocate use of one product over another, but they do recommend using individualized dose adjustments to improve effectiveness and minimize side effects

Updated Information - Growth Hormones

- Discontinuation:
  - **tesomatropin, recombinant (Humatrope), July 2020**
    - Eli Lilly reported to FDA plan to discontinue one presentation of Humatrope, the 5 mg kit (NDC 0002-7335-11), which contains 5 mg/mL in 1 vial (NDC 0002-7349-01) of Humatrope and 5 mL in 1 vial (NDC 0002-7336-01) of diluent
    - Distribution will continue until end of December 2020. Other Humatrope presentations will continue to be available

Updated Information – Growth Hormones

- **sompacitan-beco (Sogroya)**
  - **August 2020: FDA approved sompacitan-beco (Sogroya), a human growth hormone analog indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency**
  - **Indications**
    - **For replacement of endogenous growth hormone in adults with growth hormone deficiency**
  - **Precautions/Contraindications**
    - **Increased Risk of Neoplasm: There are risks of malignancy progression in patients with active malignancy and of malignant changes of preexisting nevi. Monitor patients with preexisting tumors for progression or recurrence**
    - **Glucose Intolerance and Diabetes Mellitus: Sogroya may decrease insulin sensitivity, particularly at higher doses. Monitor glucose levels periodically in all patients receiving treatment, especially in patients with existing diabetes mellitus or at risk**
    - **Contraindicated in patients with acute critical illness and/or patients with active malignancy**
  - **Dosing**
    - **Administer by subcutaneous injection to the abdomen or thigh with regular rotation of injection sites**
    - **Initiate with a dosage of 1.5 mg once weekly for treatment naïve patients and patients switching from daily growth hormone**
    - **Increase the weekly dosage every 2 to 4 weeks by approximately 0.5 mg to 1.5 mg until the desired response has been achieved**
    - **Titrate the dosage based on clinical response and serum insulin-like growth factor 1 (IGF-1) concentrations**
    - **The maximum recommended dosage is 8 mg once weekly**
  - **Formulations**
    - **Injection: 10 mg/1.5 mL (6.7 mg/mL) somapacitan-beco single-patient-use prefilled pen**

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Gastrointestinal Agents: Inflammatory Bowel Agents

Disease State Description - Ulcerative Colitis

- **Ulcerative Colitis (UC)**
  - A chronic inflammatory disease primarily affecting the colon and rectum
  - Affects approximately 1,000,000 people in the United States (US) and the incidence continues to increase worldwide
    - The Center for Disease Control and Prevention (CDC) estimates the current prevalence of UC at 238 per 100,000 adults
  - May present at any age, but onset typically peaks between 15 and 30 years of age
  - The disease is characterized by superficial infiltration of the bowel wall by inflammatory white cells, resulting in multiple mucosal ulcerations and crypt abscesses

- The predominant symptom of UC is diarrhea, which is usually associated with blood in the stool
  - Additional symptoms may include pain in the lower quadrant or rectum along with systemic features, including fever, malaise, and weight loss (which are more common if a greater portion of the colon is affected)
  - The initial attack of UC may be fulminant with bloody diarrhea, but the disease more commonly begins indolently, with non-bloody diarrhea progressing to bloody diarrhea
  - UC can present initially with any extent of anatomic involvement ranging from disease confined to the rectum to the entire large intestine (pancolitis)
  - Most commonly, UC follows a chronic intermittent course with long periods of quiescence interspersed with acute attacks lasting weeks to months. However, a significant percentage of patients suffer a chronic continuous course

Centers for Disease Control and Prevention, 2015

Treatment Guidelines - Ulcerative Colitis

American Gastroenterology Association (AGA), 2020

- Moderate to severe UC
  - Consider patients with moderate to severe disease to be those who are dependent on or refractory to corticosteroids, exhibit ulcers upon endoscopic assessment, or are at high risk for colectomy
- Long-term management can include medications from the following classes:
  - TNF-alpha antagonists, immunomodulators (e.g., thiopurines [azathioprine], methotrexate), the anti-integrin agent vedolizumab, and JAK inhibitors (e.g., tofacitinib)
  - If the agent selected for inducing remission is effective, it is usually continued as maintenance therapy; the exception to this would be when corticosteroids or cyclosporine are used for induction of remission
  - The following agents are recommended over no treatment for adult outpatients with moderate to severe UC, listed in order of FDA approval: infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab
  - In patients who are biologic-naive, infliximab or vedolizumab are suggested rather than adalimumab for induction of remission; however, patients with less severe disease who value the convenience of self-administration over the relative efficacy of therapy may select adalimumab instead
  - For induction of remission, thiopurine monotherapy is suggested against use; however, it is suggested over no treatment for maintaining remission
    - Methotrexate monotherapy is suggested against use for induction, as well as maintenance of remission
  - The combination of TNF-alpha antagonists (vedolizumab or ustekinumab) is suggested with thiopurines or methotrexate over biologic monotherapy or thiopurine monotherapy
  - Early use of biologics with or without immunomodulator therapy is suggested rather than gradual step up to these agents following failure of 5-ASA
  - Additional recommendations for adult outpatients with moderate to severe UC are provided regarding the use of tofacitinib and management of non-responders to infliximab
- For patients who achieve remission with biologic agents and/or immunomodulators or tofacitinib, it is suggested against continuing 5-ASA for induction and maintenance of remission

Treatment Guidelines

American Gastroenterology Association (AGA), 2019

- Treatment of mild to moderate UC recommend standard-dose mesalamine (2 to 3 g/day) or diazo-bonded 5-ASA (balsalazide and olsalazine) for induction and maintenance treatment
- High-dose oral mesalamine combined with rectal 5-ASA may be required for patients with suboptimal response to standard-dose therapy, or in those with moderate or extensive disease
  - Oral prednisone or budesonide MMX may be added in those refractory to optimized oral and rectal 5-ASA
- Proctosigmoiditis or proctitis can be treated with topical mesalamine rather than oral 5-ASA
  - In patients with suboptimal response or intolerance to rectal mesalamine, rectal corticosteroids (enema or foam) may be used
- Patients who do not respond adequately to the therapies as outlined above may need to escalate to systemic corticosteroids, immunomodulators, or biologic therapies
- The guidelines make no recommendations regarding the use of probiotics, curcumin, and FMT
  - While they appear to be safe, their use could delay initiation of proven efficacious treatments and potentially lead to worsening symptoms or complications

Treatment Guidelines

- **American Academy of Family Physicians (AAFP), 2013**
  - State that the incidence of colon cancer is increased with UC and achieving remission is critical in order to reduce a patient's lifetime risk
  - First-line treatment
    - Recommend 5-ASA (mesalamine) via suppository or enema for patients with proctitis or proctosigmoiditis, respectively
      - If unable to tolerate rectally administered 5-ASA therapy, may try oral preparations, although response times and remission rates are not as favorable. Oral 5-ASA is effective in patients with active mild to moderate UC extending from the proximal to the sigmoid colon
      - A topical 5-ASA may be added if an oral formulation alone is inadequate
      - A short-term course of oral corticosteroids may be appropriate if oral plus topical 5-ASA therapy is not effective or if a more rapid response is desired
      - Prednisone is given in dosages of 40 to 60 mg per day, with the full-dose continued until symptoms are completely controlled (usually 10 to 14 days) followed by a gradual taper
      - Long-term steroid use is not recommended for chronic maintenance due to significant side effects
  - To prevent relapse
    - Oral probiotics (*Lactobacillus* GG and *Escherichia coli* Nissle 1917) have been shown to be effective
    - The agent that is used to maintain remission is usually the same as that used to achieve remission
  - Symptoms refractory to oral mesalamine or oral corticosteroids may be treated with intravenous infliximab (Remicade)
  - Azathioprine is generally not recommended for active UC; however, it may be considered in patients who require corticosteroids or cyclosporine to induce remission
  - Budesonide (Uceris) was first FDA approved in January 2013 and is not specifically addressed in these guidelines

Appendices

Treatment Guidelines - Anticoagulants

American College of Chest Physicians (ACCP), 2018

- Guidelines suggest no antithrombotic therapy
  - In patients with AF without valvular heart disease, including those with paroxysmal AF, who are at low risk for stroke (CHA2DS2VASc ≥ 0 in males or ≥ 1 in females)
- Guidelines recommend oral anticoagulation therapy
  - Patients with AF, including those with paroxysmal AF, without valvular heart disease who have 1 non-sex CHA2DS2VASc stroke risk factor are suggested to receive oral anticoagulation while patients considered at high risk of stroke (e.g., CHA2DS2VASc ≥ 2 in males or ≥ 3 in females)
- Where oral anticoagulation is recommended or suggested, ACCP suggests using a novel oral anticoagulant (NOAC) rather than adjusted-dose vitamin K antagonist therapy

AHA/ACC/HRS Guidelines, 2019 Update

- All NOACs are now preferred over warfarin in NOAC-eligible patients with AF; exceptions to this are patients with moderate-to-severe mitral stenosis or a mechanical heart valve
  - In NOAC-eligible patients, NOACs were shown to be at least noninferior to warfarin in preventing stroke and systemic embolism and have a lower risk of bleeding
  - Apixaban is preferred in patients with end-stage renal disease or on dialysis while the other NOACs are not recommended in this population due to lack of evidence
  - Edoxaban is now included in the guidelines as an option for stroke prevention
  - The anticoagulant reversal agents idarucizumab (Praxbind) and andexanet alfa (Andexxa) are recommended in the event of life-threatening bleeding or an urgent procedure

Treatment Guidelines – Ulcerative Colitis

The 2019 American College of Gastroenterology (ACG)

- Clinical guidelines state treatment selection for UC should be based on not only inflammatory activity but also disease prognosis
- In patients with:
- Mildly active proctitis and distal UC are treated with rectal 5-ASA
    - Oral 5-ASA agents are used if needed as add-on for distal UC or to treat extensive disease
- Mildly active UC who are intolerant or nonresponsive to 5-ASA, oral budesonide MMX is recommended to induce remission
- Moderately active UC should be treated with oral 5-ASA or budesonide MMX
- Moderately to severely active UC, the ACG recommends induction of remission using systemic corticosteroids, anti-TNF therapy, vedolizumab, or tofacitinib
    - With the exception of corticosteroids, the medication used to induce remission should be continued as maintenance therapy
    - The ACG states that complimentary therapies such as probiotics, curcumin, and fecal microbiota transplantation (FMT) require further study and clarification of treatment/end points