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Formulary Update

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Teplizumab Delays the Onset of Stage 3 Type 1 Diabetes

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Background: Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by insulin deficiency and hyperglycemia due to the destruction of pancreatic beta cells.[1] Each year it is estimated that 64,000 individuals in the U.S. are diagnosed with T1D.[2] The peak age of diagnosis is around 13 to 14 years old.[3] Over time, an immune-mediated loss of functional pancreatic beta cells leads to symptomatic diabetes and irreversible insulin dependence.[1] It has been hypothesized that CD8+ T lymphocytes play a major role in the gradual destruction of these pancreatic beta cells.[4] New literature surrounding T1D has found that the disease begins well before its symptomatic manifestations and a staging classification system has been proposed to categorize the earliest stages of this disease state and to delineate the lifetime risk of developing symptomatic T1D.[1,4] Stage 1 includes pre-symptomatic patients with two or more T1D-associated pancreatic islet autoantibodies and normal blood glucose levels. The risk of developing diabetes at this stage varies, with the 5-year and 10-year risks being 44% and 70%, respectively and a lifetime risk of nearly 100%. Stage 2 includes pre-symptomatic patients with two or more autoantibodies and abnormal glucose tolerance or dysglycemia, but not overt hyperglycemia. The 5-year risk of symptomatic disease at this stage is 75% with a lifetime risk of nearly 100%. Stage 3 , also referred to as clinical T1D, includes patients with classic symptoms of hyperglycemia or hyperglycemic crisis characterized by one of the following diagnostic criteria: fasting plasma glucose (FBG) ≥126 mg/dL; 2-hour postprandial glucose ≥200 mg/dL during an oral glucose tolerance test (OGTT); glycosylated hemoglobin ≥6.5% or random plasma glucose ≥200 mg/dL.[1,5] Teplizumab-mzwv (Tzield™; Provention Bio, Inc.) was recently approved by the Food and Drug Administration (FDA) in November 2022 to delay the onset of Stage 3 T1D in adult and pediatric patients 8 years and older with Stage 2 T1D.[6] The diagnosis of Stage 2 T1D must be established by confirmation of at least two positive pancreatic islet cell autoantibody tests and symptoms of dysglycemia without overt hyperglycemia using an OGTT. Additionally, the patient's clinical history should not suggest type 2 diabetes.

Mechanism of Action: Teplizumab is a novel anti-CD3 antibody that binds to CD3 surface antigens on CD4+ and CD8+ T cells, which leads to an increase in regulatory T cells and a depletion of CD8+ T cells in peripheral blood.[4,6] The mechanism for delaying the progression of Stage 2 to Stage 3 T1D is thought to involve partial agonistic signaling and deactivation of pancreatic beta cell autoreactive T lymphocytes.

Clinical Trial: The safety and efficacy of teplizumab were investigated in a Phase 2, multi-center, international, randomized, double-

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blind, event-driven, placebo-controlled trial.[4] First- or second-degree relatives of individuals with T1D, identified through the TrialNet Study Group, were included in this study. These participants needed to have two or more diabetes-related autoantibodies detected in two samples obtained within 6 months before randomization and evidence of dysglycemia (e.g., elevated FBG). There were 76 patients included in the study ranging from 8 to 45 years old with Stage 2 T1D. Patients were randomized to receive teplizumab (n=44) or placebo (n=32) once daily intravenously for 14 days. The primary endpoint was the time elapsed from randomization to clinical diagnosis of T1D. In this study, 45% of patients were female, 97% were White, 1% were Asian, 1% were multiracial and 3% were Hispanic or Latino. The median patient age was 14 years old with 72% under the age of 18. Patients received the following dosing regimen: Day 1: 51 mcg/m^2, Day 2: 103 mcg/m^2, Day 3: 207 mcg/m^2, Day 4: 413 mcg/m^2, and Days 5-14: 826 mcg/m^2. The data were analyzed using a Cox proportional hazards model stratified by age and OGTT. Stage 3 T1D was diagnosed in 43% of the patients in the teplizumab group and 72% of the patients in the placebo group. The median time from randomization to a diagnosis of Stage 3 T1D was 48.4 months in the teplizumab group and 24.4 months in the placebo group. Teplizumab treatment resulted in a statistically significant delay in time to the development of Stage 3 T1D (hazard ratio, 0.41;95% CI: 0.22 to 0.78; p=0.006). The hazard ratio remained significant when adjusted for age and OGTT. The most common side effects in teplizumab-treated patients were lymphopenia (75%), dermatologic rash (36%), pain (11%), and infection (11%). The authors concluded that a 14-day course of teplizumab delayed the diagnosis of clinical T1D in high-risk patients.

Dosing and Administration: Teplizumab is administered via intravenous infusion over a minimum of 30 minutes once daily for 14 consecutive days.[6,7] Two doses should not be given on the same day. If a planned dose is missed, the remaining doses should be resumed on consecutive days to complete the treatment course. The dosing schedule is as follows:

- Day 1: 65 mcg/m^2
- Day 2: 125 mcg/m^2
- Day 3: 250 mcg/m^2
- Day 4: 500 mcg/m^2
- Days 5-14: 1030 mcg/m^2

This FDA-approved dosing differs from what was utilized in the phase 2 trial, since a different manufacturer acquired the drug and changed its formulation.[8] The new formulation was found to have increased clearance, thus necessitating new dosage recommendations. A pre-medication regimen consisting of a nonsteroidal anti-inflammatory drug or acetaminophen, an antihistamine, and/or an antiemetic must be given before the teplizumab infusion is administered for the first 5 days of the 14-day course of therapy.[6,7]

Cost and Availability: Teplizumab is available as a single-dose vial (2mg/2mL) NDC 73650-316-01.[6] The average wholesale price is $16,620 per vial.[7] The average cost of a full course of therapy will be approximately $232,680 (one vial per dose).

Formulary Status: Teplizumab has been added to the CCHS Pediatric Formulary for outpatient use only for patients who meet all of the following criteria:

1. ≥8 years of age
2. Have relative with type 1 diabetes
3. Have two or more diabetes autoantibodies
4. Have Stage 2 diabetes

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Alpha-1-Proteinase Inhibitor (human) (Zemaira®) Injection	Antitrypsin Deficiency Agent	Acute Steroid Refractory GVHD	Restricted to Hematology/ Oncology for patients with acute, steroid refractory GVHD
Cabotegravir (Apretude®) Injection	Antiretroviral Agent	HIV Pre-Exposure Prophylaxis	
Fecal Microbiota, live-jsim (Rebyota™) Rectal Suspension	Microbiota	CD Infection Prophylaxis	Restricted to the Department of Gastroenterology for out-patient use only
Lenacapavir (Sunlenca®) Tablets/Subcutaneous Injection	Antiretroviral Agent	HIV Infection Treatment	
Mirvetuximab-Soravtansine-gynx (Elahere®) Injection	Monoclonal Antibody	Platinum-Resistant Ovarian Cancer	Restricted to the Department of Gynecologic Oncology for outpatient use only
Mosunetuzumab-axgb (Lunsumio®) Injection	Monoclonal Antibody	Relapsed/Refractory Follicular Lymphoma	Restricted to the Department of Hematology/Oncology for outpatient use only

GVHD=Graft versus Host Disease HIV=Human immunodeficiency virus CD=Clostridium difficile

Denial to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Rationale**
Dexmedetomidine (Igalmi™) Sublingual Film	Alpha$_2$-Adrenergic Agonist	Agitation associated with Schizophrenia or Bipolar I or II disorder	A decision was made not to add dexmedetomidine sublingual film due to difficulty administering to an agitated patient

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions/ Comments**
Ceftazidime (Fortaz®) Injection	Antibiotic	Various Infections	Modify restriction to include the Department of Nephrology for intraperitoneal administration Nephrology providers can order a one-time dose of IV ceftazidime prior to intraperitoneal administration
Fosaprepitant Dimeglumine (Emend®) Injection	Anti-emetic	PONV	Modify restriction to state: Restricted to the Department of Anesthesiology for the treatment of severe PONV non-responsive to multiple pre-emptive and rescue anti-emetics and in patients with severe QT prolongation
Hydroxyurea (Hydrea®) Capsules and Tretinoin Capsules (ATRA)	Antineoplastic Agent	AML APL	APPs may order initial doses of hydroxyurea and tretinoin with documentation of collaboration with a Staff Oncologist included in the order
Molnupiravir (Lagevrio®) Capsules Nirmatrelvir/ Ritonavir (Paxlovid™) Tablets	Antiviral Agent	COVID-19 Treatment	Modify restriction criteria to remove the requirement of a positive SARS-CoV-2 test for high-risk inpatient and outpatient adults and requiring treatment for mild-moderate COVD-19 infection
Siltuximab (Sylvant®) Injection	Monoclonal Antibody	IMCD	Modify restrictions to include use by Hematology/Oncology for IMCD for outpatient use only
Ziprasidone Mesylate (Geodon®) Injection	Antipsychotic	Agitation	Modified restriction to include Neurology

IV=Intravenous PONV=Postoperative nausea and vomiting ATRA=All-trans retinoic acid AML=Acute myeloid leukemia APL=Acute promyelocytic leukemia APP=Advanced practice providers COVID-19=Coronavirus disease-2019 SARS-CoV-2=Severe acute respiratory syndrome coronavirus-2 IMCD=Idiopathic Multicentric Castleman Disease

Product Standardizations to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Details**
Angiotensin II Receptor Blockers	Antihypertensive	Hypertension CHF	A therapeutic interchange has been created for ARBs Details are in Lexicomp
Inhaled Corticosteroid/Long-Acting Beta Agonist	Corticosteroid/ Beta Agonist	Asthma COPD	The preferred ICS/LABA inhaler for the therapeutic interchange for patients not mechanically ventilated and not in the ED or Obs unit has changed from fluticasone/ vilanterol (Breo®Ellipta®) to mometasone/formoterol (Dulera®) Details are in Lexicomp

CHF=Congestive heart failure ARBs=Angiotensin II receptor blockers ICS/LABA=Inhaled corticosteroid/long-acting beta agonist
COPD=Chronic obstructive pulmonary disease ED=Emergency department Obs=Observation

Process Changes to the Adult CCHS Formulary			
Process	**Pharmacologic Class**	**Formulary Use**	**Details**
Medication Dose Optimization and Monitoring Standard Operating Procedure	Various Classes	Various Indications	Pharmacists will be able to autonomously change the doses of select medications based on the patient's renal function. Details will be provided at a later date.
Pharmacist Managed Intravenous to Oral Medications Standard Operating Procedure	Various Classes	Various Indications	Pharmacists will be able to autonomously convert select medications from IV to oral when a patient meets certain criteria. Details will be provided at a later date.
Push-Dose Epinephrine Epic Panel	Vasopressor	Allergic Reactions Anaphylaxis	An epinephrine Epic Order Panel was created so that the prescriber can select the appropriate epinephrine for the correct indication. The order panel contains the following selections: 1) Epinephrine Intravenous Infusion 2) Epinephrine 1 mg/mL 1 mL IM injection for allergic reactions/ anaphylaxis 3) Epinephrine 10 mcg/mL 10 mL injection as a push-dose pressor*

*May only be given in areas that support the use of push-dose intravenous epinephrine. Administration instructions will state: Must be administered with physician at the bedside.
IV=Intravenous IM=Intramuscular

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Betibeglogene Autotemcel (Zynteglo®) Injection	Gene Therapy	Beta-thalassemia	Restricted to Staff Physicians from the Department of Pediatric Bone Marrow Transplant for patients who meet the following criteria: 1) Pediatric patients with beta-thalassemia who require regular red blood cell transfusions 2) Only after prior authorization or covered approval has been obtained from the patient's insurance company in conjunction with the manufacturer
Bupivacaine Liposomal (Exparel®) Injection	Local Anesthetic	Analgesia of Incisional Wounds	Restricted to pediatric patients 6 years of age and older for local infiltration of incisional wounds for prolonged analgesia
Ferumoxtyol (Feraheme®) Injection	Iron Supplement	Iron Deficiency Anemia	Restricted to Pediatric Cardiology for the use in the following populations: 1) For patients with known or suspected pediatric or congential heart disease, for optimal evaluation of intracardiac and/or extracardiac anatomy 2) For patients with a history of allergic reactions to GBCAs
Olipudase alfa-rpcp (Xenpozyme™) Injection	Enzyme	ASMD	Restricted to Pediatric Hematology/Oncology for outpatient use only
Teplizumab-mzwv (Tzield™) Injection	Monoclonal Antibody	Delaying onset of Stage 3 T1D	Restricted to Pediatric Endocrinology for outpatient use only for patients that meet all of the following criteria: 1) 8 years of age and older 2) Have a relative with type 1 diabetes 3) Have two or more diabetes autoantibodies 4) Have Stage 2 diabetes*

*Stage 2 diabetes is having dysglycemia such as impaired fasting glucose, impaired glucose tolerance, or a hemoglobin A1C that is elevated but not in diabetes range.

GBCAs=Gadolinium-based contrast agents ASMD=Acid sphingomyelinase deficiency T1D=Type 1 diabetes

Changes to Restrictions of the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes**
Antithymocyte Globulin, equine (Atgam®) Injection	Immune Globulin	Various Indications	Modified restrictions to restrict use to Hematology/Oncology and Bone Marrow Transplant, and Transplant Services for patients who are unable to tolerate antithymocyte globulin, rabbit (Thymoglobulin®)
Ceftazidime (Fortaz®) Injection	Antibiotic	Various Infections	Modified restrictions to include the Department of Nephrology for intraperitoneal administration. Nephrology providers can order a one-time dose of IV ceftazidime prior to intraperitoneal administration
Nirmatrelvir/Ritonavir (Paxlovid™) Tablets	Antiviral	COVID-19 Infection	Modified restrictions to remove the requirement of a positive SARS-CoV-2 test for high-risk inpatients and outpatient pediatric patients (12 years and older and at least 40 kg) requiring treatment of mild-to-moderate COVID-19 infection.

IV=Intravenous COVID-19=Coronavirus disease-2019 SARS-CoV-2=Severe acute respiratory syndrome coronavirus-2
kg=kilograms

Process Changes to the Pediatric CCHS Formulary			
Process	**Pharmacologic Class**	**Formulary Use**	**Details**
Medication Dose Optimization and Monitoring Standard Operating Procedure	Various Classes	Various Indications	Pharmacists will be able to autonomously change the doses of select medications based on the patient's renal function.* Details will be provided at a later date.

*The Standard Operating Procedure has a separate list of Medications for Pharmacist-Initiated Adjustment in Pediatric Patients and Medications for Pharmacist-Initiated Adjustment in Adult Patients