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Aprocitentan for Resistant Hypertension

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Background: Resistant hypertension (RH), a condition associated with an increased cardiovascular risk, is defined as above-goal elevated blood pressure (BP) despite the concurrent use of three or more antihypertensives, commonly including a long-acting calcium channel blocker, an angiotensin-converting enzyme inhibitor or receptor blocker, and a diuretic at the maximum or maximally tolerated doses or the use of four or more antihypertensives regardless of BP level.[1,2] The American Heart Association's 2018 Scientific Statement indicated that approximately 10.3 million US adults met the criteria for RH.[1] The endothelin (ET) pathway plays a significant role in the pathogenesis of volume and salt-dependent forms of RH, however, it has not been previously targeted by antihypertensive medications.[3,4] Therefore, aprocitentan, a dual endothelin receptor antagonist (ERA), was evaluated for its efficacy in treating elevated BP in a phase 2 clinical trial.[5] This trial demonstrated that aprocitentan monotherapy produced a significant reduction in BP in patients with mild-to-moderate hypertension. Consequently, PRECISION, a Phase 3 clinical trial, was conducted to determine aprocitentan's efficacy and safety as a part of combination therapy for RH.[3] Based on the results of that study, aprocitentan (Tryvio®; Idorsia Pharmaceutical) was approved by the Food and Drug Administration (FDA) in March 2024 for the treatment of hypertension in combination with other antihypertensive drugs to lower BP in adult patients not adequately controlled on other medications.[6]

Mechanism of Action: The binding of ET-1 to its receptors, ET_A and ET_B can precipitate hypertension by enhancing endothelial dysfunction, vascular hypertrophy and remodeling, sympathetic nervous system activation, and enhanced aldosterone production.[6] Aprocitentan, a dual endothelin ERA, blocks the attachment of ET-1 to its receptors, thus lessening these hypertensive effects.

Clinical Trial: The PRECISION study was a multi-center, blinded, randomized, parallel-group, phase 3 study to determine whether aprocitentan, added to three antihypertensives of different pharmacologic classes, produced a significant reduction in BP compared with placebo in patients with RH and whether this effect could be sustained for up to 40 weeks.[3] Eligible participants had an uncontrolled, sitting systolic BP of ≥ 140 mm Hg despite taking at least three antihypertensive medications including a diuretic for at least 1 year before screening. Unattended automated office blood pressure readings were done at each visit and 24-hour ambulatory BP monitoring (ABPM) was performed at specific intervals. Adverse events were recorded throughout the study. During screening, all patients were switched from their individual antihypertensive regimens (except beta

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blockers) to a standardized therapy consisting of a single-pill triple combination of amlodipine, valsartan, and hydrochlorothiazide at fixed doses of either 5 mg/160 mg/25 mg or 10 mg/160 mg/25 mg. The maximally tolerated standardized doses were utilized. The active treatment study period, which lasted 48 weeks, was divided into three consecutive parts in which aprocitentan or placebo was administered as add-on therapy. Part 1 was a 4-week double-blind, randomized, placebo-controlled segment in which patients were assigned to receive either aprocitentan 12.5 mg, aprocitentan 25 mg, or a placebo in equal proportions (1:1:1). Part 2 was a 32-week single-blind sequence in which all patients were assigned to receive aprocitentan 25 mg. Part 3 spanning 12 weeks was the withdrawal part of the active treatment period in which patients were re-randomized to receive either aprocitentan 25 mg or a placebo at a 1:1 ratio. The primary and key secondary endpoints were changes in the mean trough sitting systolic blood pressure (SBP) from baseline to week 4 (Part 1) and from withdrawal baseline (week 36) to week 40 (Part 3), respectively. Seven-hundred and four patients completed part 1, 613 completed part 2, and 577 completed part 3. The least square mean (SE) change in office SBP at 4 weeks was -15.3 (0.9) mm Hg, -15.2 (0.9) mm Hg, and -11.5 (0.9) mm Hg for aprocitentan 12.5 mg, 25 mg, and placebo groups, respectively. The difference of the aprocitentan 12.5 mg and 25 mg compared to placebo was -3.8 (1.3) mm Hg (97.5% confidence interval (CI): -6.8 to -0.8; p=0.0042) and -3.7 (1.3) mm Hg (97.5% CI: -6.7 to -0.8; p=0.0046), respectively. For the secondary endpoint, office SBP after 4 weeks of withdrawal, the SBP increased significantly with placebo compared with aprocitentan (5.8 mm Hg difference; 95% CI: 3.7 to 7.9; p<0.0001). The most frequent adverse event was mild-to-moderate edema or fluid retention which occurred in 9%, 18%, and 2% of those who received aprocitentan 12.5 mg, 25 mg, and placebo, respectively. The authors concluded that in patients with RH, aprocitentan was superior to placebo in reducing BP at week 4 with a sustained effect at week 40 and was generally well tolerated.

Safety: The most common adverse reactions occurring in ≥2% of patients treated with aprocitentan were edema/fluid retention and anemia.[6] The drug could cause hepatotoxicity, and therefore, it is recommended that baseline serum aminotransferase levels and total bilirubin be repeated periodically during treatment and as clinically necessary. Aprocitentan carries a black box warning for fetal-embryo toxicity. Prescribers and patients must be enrolled in a Risk Evaluation Mitigation Strategy (REMS) program.

Dosing and Administration: The FDA-approved dose of aprocitentan is 12.5 mg once daily with or without food.[6] The drug should be initiated in females of childbearing age only after confirmation of a negative pregnancy test. Negative pregnancy tests need to be confirmed monthly during treatment and 1 month after discontinuation. The package insert outlines specific recommendations for patients to prevent pregnancy during their course of therapy. Aprocitentan is not recommended in patients with renal failure (eGFR < 15 mL/min) or on dialysis and those with moderate or severe hepatic impairment (Child-Pugh class B and C). There are no dosage adjustments for patients with severe renal impairment and for those with mild hepatic impairment (Child-Pugh class A).

Cost and Availability: Tryvio® 12.5 mg film-coated tablets are available as blister packs containing 10 tablets (NDC 80491-8012-8) or as bottles containing 30 tablets (NDC 80491-8012-13).[6] Tryvio® may be purchased through Walgreens Specialty Pharmacy.[7] Each 12.5 mg tablet costs approximately $31, so a 1-month supply would be about $960.

Formulary Status: Aprocitentan (Tryvio®) is not currently on the CCHS Adult Formulary.

References:

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2. Carey, RM, Calhoun, DA, Bakris, GL, et al. Resistant hypertension: detection, evaluation, and management: A scientific statement from the American Heart Association. Hypertension, 2018;72(5), e53-e90.
3. Schlaich MP, Bellet M, Weber MA, et al. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial 2022;400:1927-37.
4. Danietas P, Verweij P, Wang J et al. Investigating the endothelin receptor antagonist aprocitentan in resistant hypertension: design and baseline characteristics of the PRECISION study. European Heart Journal. 2021;42(Supplement_1).
5. Verweij P, Danaietash P, Flamion B et al. Randomized dose-response study of the new dual endothelin receptor antagonist aprocitentan in hypertension. Hypertension. 2020;75(4):956-65.
6. Aprocitentan [package insert]. Radnor PA: Idorsia Pharmaceutical; March 2024.
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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Afamitresgene Autoleucel (Tecelra®) Intravenous Injection	Cellular Immunotherapy	Unresectable or Metastatic Synovial Sarcoma	Restricted to the Departments of Hematology/Oncology and Bone Marrow Transplantation
Antiparasitic Agents (albendazole, nitazoxanide, paromomycin, praziquantel)	Antiparasitic Agents	Pathogen-directed Parasitic Infections	Nitazoxanide, Paromomycin, and Praziquantel will be restricted to Infectious Diseases. Albendazole is not restricted. Dose rounding of these agents is included in Up-to-Date® Lexidrug™. These agents are excluded from the Dose Optimization Pharmacy Consult Service for both adult and pediatric patients.
Buprenorphine (Brixadi®) Extended-Release Subcutaneous Injection	Opioid Partial Agonist	Opioid Use Disorder	Restricted to providers within Adult Behavioral Health for the treatment of opioid use disorder in adult patients and will be limited to outpatient use only Compliance with all of the REMS Program requirements for Brixadi® must be ensured prior to dispensing the corresponding extended-release buprenorphine injection. Note: The restriction criteria for Sublocade® will be modified to mimic the restriction criteria for Brixadi®.
Degarelix (Firmagon®) Subcutaneous Injection	GnRH Antagonist	Advanced Prostrate Cancer	Restricted to the Department of Hematology/Oncology for the treatment of patients with prostrate cancer unable to receive a GnRH agonist for treatment initiation due to the risk of clinical tumor flare (for a total of 1 month or one dose); restricted to outpatient use only. Note: The degarelix 240 mg kit will be the only product on Formulary (i.e., the 80 mg kit remains non-formulary.)
Delandistrogene-moxeparvovec-rokl (Elevidys®) Intravenous Injection	Gene Therapy	Duchenne Muscular Dystrophy	Restricted to the Department of Neurology for outpatient use only

REMS=Risk evaluation mitigation strategy GnRH=Gonadotropin-releasing hormone

Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Donanemab-azbt (Kisunla™) Intravenous Injection	Anti-Amyloid Monoclonal Antibody	Alzheimer's Disease	Restricted to the Center for Brain Health for outpatient use only in a formalized protocol Note: In the enterprise, cognitive neurologists not part of the Center for Brain Health may also prescribe donanemab in the outpatient setting under this formalized protocol (i.e., are able to meet all aspects of the formalized protocol including monitoring and managing of adverse drug reactions).
Guselkumab (Tremfya®) Intravenous Injection	Interleukin-23 Inhibitor	Moderate-to-Severe Ulcerative Colitis	Restricted to the Department of Gastroenterology for the management of ulcerative colitis for outpatient use only Note: Guselkumab subcutaneous injection remains non-formulary.
Obecabtagene Autoleucel (Aucatzyl®) Intravenous Injection	CAR-T Immunotherapy	R/R Precursor ALL	Restricted to the Department of Hematology/Oncology and Bone Marrow Transplantation
Ocrelizumab and Hyaluronidase-ocsq (Ocrevus Zunovo™) Subcutaneous Injection	Anti-CD20 Monoclonal Antibody	Various forms of Multiple Sclerosis	Restricted to the Department of Neurology for outpatient use only
Zolbetuximab-clzb (Vyloy®) Intravenous Injection	Anti-CLDN 18.2 Monoclonal Antibody	CLDN18.2 positive/ HER2 negative Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma	Restricted to the Department of Hematology/Oncology in patients unable to tolerate and/or unlikely to benefit from immune checkpoint inhibitors; restricted to outpatient use only Note: Dose rounding of zolbetuximab-clzb was approved as follows: round to the nearest vial if within 10%.

CAR-T=Chimeric antigen receptor T-cell R/R=Relapse or refractory ALL=Acute lymphoblastic leukemia
HER2=Human epidermal growth factor receptor 2

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions/ Comments**
Buprenorphine (Sublocade®) Extended-Release Subcutaneous Injection	Opioid Partial Agonist	Opioid Use Disorder	Please refer to Adult Formulary Addition Table
Dalbavancin (Dalvance®) Intravenous Injection	Antimicrobial Agent	Various Infections	Restricted to the Department of Infectious Diseases for the following indications: 1. Inpatient setting for pathogen-directed osteoarticular and endovascular infections as a bridge to outpatient therapy. 2. Outpatient setting for pathogen-directed treatment of ABSSSI, osteoarticular, and endovascular infections in patients who are not candidates for formulary CCHS agents and with insurance approval for dalbavancin. 3. Florida Region Hospital-at-Home with Infectious Disease consult. 4. Emergency Department Ohio East Region (Marymount, Mentor, Hillcrest ED) for acute bacterial skin and soft tissue infection.
DaxibotulinumA (Daxxify®) Intramuscular Injection	Neuromuscular Blocker	Cervical Dystonia	Modified restrictions to include the Department of Neurology for treatment of cervical dystonia in the outpatient setting
Droperidol Intravenous Injection	Dopamine D2 Receptor Agonist	Antiemetic	Modified restrictions to allow for droperidol to be administered outside of an ICU-designated unit if a patient is in a monitored unit (telemetry) and a baseline EKG is obtained (regardless of one-time dose or multiple doses)
Efgartigimod alfa and Hyaluronidase-qvfc (Vyvgart® Hytrulo) Subcutaneous Injection	Neonatal Fc Receptor Antagonist	CIDP	Modified restrictions to include the Department of Neurology for use in patients with CIDP in the outpatient setting

ABSSSI=Acute bacterial skin and skin structure infections ED=Emergency department ICU=Intensive care unit EKG=Electrocardiogram CIDP=Chronic inflammatory demyelinating polyneuropathy

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions/ Comments**
Fibrinogen Concentrate, Human (RiaSTAP®) Intravenous Injection	Blood Product Derivative	Congenital Fibrinogen Deficiency	Modified restrictions to include patients undergoing major cardiac, vascular, and thoracic surgery that refuse to accept cryoprecipitate Criteria for use in these patients will be restricted to ordering by Hematology or by Staff Anesthesia in consultation with Hematology for the indications of low fibrinogen and clinically significant bleeding attributable to low fibrinogen.
IncobotulinumtoxinA (Xeomin®) Intramuscular Injection	Neuromuscular Blocker	Laryngeal Dystonia	Modified restrictions to include the Department of Otolaryngology for use in the outpatient setting
Nifedipine Immediate-Release Capsules	Calcium Channel Blocker	Tocolytic Therapy	Modified restrictions to include use by the Department of Obstetrics for tocolysis
Rifaximin (Xifaxan®) Tablet	Rifamycin	Hepatic Encephalopathy	When used for hepatic encephalopathy, rifaximin is restricted to inpatients not receiving broad-spectrum antibiotics. Note: Rifaximin use is not restricted for other indications.
Tarlatamab-dlle (Imdelltra™) Intravenous Injection	Bispecific Monoclonal Antibody	Cancers with small cell histology	Modified restrictions to include use by Gynecology/Oncology
Tocilizumab (Actemra®) Intravenous Injection	Monoclonal Antibody	CRS	Modified restrictions (when utilized for CRS) to state: Restricted for the management of CRS Note: This modification removes the verbiage about services it is restricted to, prescriber restrictions, and need for Hematology/Oncology consult

CRS=Cytokine-release syndrome

Product Standardization and Process Changes to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Details**
Moxifloxacin (oral and IV formulations)	Antibiotic	Infections caused by Mycobacteria spp., Nocardia spp, and M. genitalium	Site-specific therapeutic interchanges that automatically substitute moxifloxacin for levofloxacin will be removed. Moxifloxacin will remain on Formulary at all sites, with no automatic substitutions to levofloxacin.
Oncology SOP for Pharmacy Consult Agreement	Oncology Medications	Plasma Cell Disorders Bone Marrow Transplant Lymphoma Leukemia Solid Tumors	Updates to consult agreement: 1. The expansion of this agreement to sites outside of Main Campus (i.e., the Enterprise). 2. The addition of a disease state: Solid Tumor Oncology

SOP=Standard operating procedure

Denial to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Details**
Tinidazole Tablet	Antiparasitic Agent	Parasitic Infections	A DUE indicated that tinidazole use was primarily for off-label management of IBD and not for parasitic infections.

DUE=Drug use evaluation IBD=Inflammatory bowel disease

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Antiparasitic Agents (albendazole, nitazoxanide, paromomycin, praziquantel)	Antiparasitic Agents	Pathogen-directed Parasitic Infections	Nitazoxanide, Paromomycin, and Praziquantel will be restricted to Infectious Diseases. Albendazole is not restricted. Dose rounding of these agents is included in Up-to-Date® Lexidrug™. These agents are excluded from the Dose Optimization Pharmacy Consult Service for both adult and pediatric patients.
Dapagliflozin (Farxiga®) Tablet	SGLT2 Inhibitor	Heart Failure	Restricted as follows: 1. Initiation of therapy for heart function use is restricted to the Department of Cardiology. 2. Continuation of therapy from home is not restricted.
Delandistrogene-moxeparvovec-rokl (Elevidys®) Intravenous Injection	Gene Therapy	Duchenne Muscular Dystrophy	Restricted to Staff Physicians from the Department of Pediatric Neurology for outpatient use only after prior authorization or covered approval has been obtained from the patient's insurance in conjunction with the manufacturer.
Imatinib (Gleevec™) Tablet	Tyrosine Kinase Inhibitor	CML ALL PVS	Restricted as follows: Initiation of therapy for PVS is restricted as follows: 1. Eligible patients will be identified by Pediatric Cardiology or Pediatric Cardiac Intensive Care Unit providers AND 2. Will require a Pediatric Hematology/Oncology consult 3. Order must be placed by a Pediatric Hematology/Oncology Staff Physician Continuation of therapy from home orders require order entry by a Pediatric Hematology/Oncology Staff Physician 1. Agents that may be used as oral chemotherapy require order entry by a Staff Physician. Includes initial dose, continuation, discontinuation, and modification.

SGLT2=Sodium-glucose cotransporter-2 CML=Chronic myeloid leukemia AML=Acute lymphoblastic leukemia PVS=Pulmonary vein stenosis

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Selexipag (Uptravi®) Tablet	Selective Prostacyclin Receptor Agonist	PAH	Restricted as follows: 1. Initiation of therapy is restricted to Staff Physicians and Fellows from the Departments of Pediatric Cardiology and Pulmonology. 2. Continuation of therapy from home is not restricted.
Treprostinil (Orenitram®) Extended-Release Tablet	Direct Vasodilator	PAH	Restricted as follows: **Initiation is restricted to patients with recommendation from the Pediatric Pulmonary Hypertension Team** 1. Orders can be placed by any prescriber, including residents. **Continuation of therapy from home is not restricted.** 1. Orders can be placed by any presriber, including residents.

PAH=Pulmonary arterial hypertension

Denial to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Details**
Tinidazole Tablet	Antiparasitic Agent	Parasitic Infections	A DUE indicated that tinidazole use was primarily for off-label management of IBD and not for parasitic infections.

DUE=Drug use evaluation IBD=Inflammatory bowel disease

Product Standardization to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Details**
Moxifloxacin (oral and IV formulations)	Antibiotic	Infections caused by Mycobacteria spp., Nocardia spp, and M. genitalium	Site-specific therapeutic interchanges that automatically substitute moxifloxacin for levofloxacin will be removed. Moxifloxacin will remain on Formulary at all sites, with no automatic substitutions to levofloxacin.

Changes to Restrictions of the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions/ Comments**
Bevacizumab (Avastin®) Intravenous Injection	Monoclonal Antibody	PVS	Restricted as follows: Initiation of therapy for PVS is restricted as follows: 1. Eligible patients will be identified by Pediatric Cardiology or Pediatric Cardiac Intensive Care Unit providers AND 2. Will require a Pediatric Hematology/Oncology consult 3. Order must be placed by a Pediatric Hematology/Oncology Staff Physician
Sildenafil (Revatio®) Tablet Intravenous Injection	Phosphodiesterase-5 Enzyme Inhibitor	PAH	**Modified restrictions for IV sildenafil as follows**: 1. Initiation is restricted to patients with recommendation from the Pediatric Pulmonary Hypertension Team* 2. Conversion from oral sildenafil to IV sildenafil is restricted to patients with recommendation from the Pediatric Pulmonary Hypertension Team* **Modified restrictions for oral sildenafil as follows**: 1. Initiation is restricted to patients with recommendation from the Pediatric Pulmonary Hypertension Team* 2. All oral sildenafil dose adjustments must be recommended by the Pediatric Pulmonary Hypertension Team* **3.** Continuation of therapy is not restricted. (Does not require recommendation by the Pulmonary Hypertension Team)+

PVS=Pulmonary vein stenosis PAH=Pulmonary arterial hypertension IV=Intravenous
*Can be ordered on any pediatric unit by any certified provider (including residents) after recommendation made by the Pulmonary Hypertension Team.
+Can be ordered on any pediatric unit by any certified provider (including residents).

Process Changes to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes**
Infliximab-dyyp (Inflectra®) Intravenous Injection Biosimilar Conversion	Monoclonal Antibody	IBD	Infliximab-dyyp (Inflectra®) will be the preferred infliximab product on the CCHS Pediatric Formulary for both inpatient and outpatient use unless insurance mandates use of Renflexis®, Avsola®, or unbranded infliximab.
Methylnaltrexone (Relistor®) Off-Label Intravenous Administration	Peripheral-Acting Opioid Receptor Antagonist	OIC	Restricted as follows: The Departments of Pediatric Gastroenterology, Pain Management, Hematology/Oncology, Palliative Medicine, and Pediatric ICU for use in patients currently on opioid therapy who have failed at least two scheduled (e.g., not PRN) and administered laxative agents for 48 hours, or patients are NPO. Patients will be limited to two doses of methylnaltrexone. 1. IV administration is limited to patients on vasoactive support for whom subcutaneous absorption may be poor.
Oral Liquid Rounding	Various	Various	Updates to Rounding Protocol 1. For all doses < 0.2 mL, round to the nearest 0.01 mL 2. For all doses between 0.2 to 1 mL, round to the nearest **0.01 mL** (was previously 0.05 mL) 3. For all doses between 1.01 to 10 mL ,round to the nearest **0.1 mL** (was previously 0.2 mL) 4. For all doses between 10.01 to 20 mL, round to the nearest 0.5 mL 5. For all doses > 20 mL, round to the nearest 1 mL

IBD=Inflammatory bowel disorder OIC=Opioid-induced constipation ICU=Intensive care unit PRN=As needed NPO=Nothing by mouth IV=Intravenous