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Risankizumab for Crohn's Disease

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Background: Crohn's disease (CD) is a chronic autoimmune disorder that is characterized by transmural inflammation of the gastrointestinal tract.[1]The prevalence of CD was estimated as 201 per 100,000 population, affecting approximately 436,000 adults in the United States.[2] Typical symptoms of CD include abdominal pain, fatigue, diarrhea and weight loss. The disease can progress over time causing intestinal strictures, abscesses, or fistulas requiring surgical intervention.[3] Biologic agents such as tumor necrosis factor (TNF) blockers (e.g., adalimumab, certolizumab, infliximab) and other anti-inflammatory therapies (natalizumab, vedolizumab, and ustekinumab) have been used to treat CD.[4] However, up to 40% of patients do not initially respond to TNF blockers and many receiving these agents will experience loss of drug efficacy or adverse events requiring discontinuation of therapy.[5,6] Among those who failed TNF therapy, 47% will not respond to vedolizumab.[6] Another biologic alternative for CD, risankizumab-rzaa (Skyrizi®; AbbVie, Inc.) was recently approved by the Food and Drug Administration (FDA) in June 2022 to treat moderately to severely active CD.[7]

Mechanism of Action: Risankizumab is a novel humanized monoclonal antibody.[7,8] It selectively binds to the p19 subunit of interleukin-23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor, reducing the release of pro-inflammatory cytokines and chemokines.

Clinical Trials: The ADVANCE and MOTIVATE studies were phase III, randomized, double-blind, placebo-controlled trials that evaluated the efficacy and safety of risankizumab as induction therapy in patients with moderately to severely active CD.[9] The Crohn's Disease Activity Index (CDAI) is often used in clinical trials to quantify subjective symptoms of CD. The CDAI score ranges between 0 and 600 with greater scores indicating more severe disease. Clinical remission is defined as a score of <150, while a score of 220-450 indicates moderately to severely active disease. In the ADVANCE trial, patients (N=931) who demonstrated an inadequate response or intolerance to prior conventional and/or biologic therapy were randomized 2:2:1 to receive intravenous (IV) risankizumab 600 mg (n=373), IV risankizumab 1200 mg, (n=372), or placebo (n=186) at weeks 0, 4, and 8. In the MOTIVATE trial, patients (N=618) who demonstrated an inadequate response or intolerance to prior biologic therapy were randomized 1:1:1 to receive IV risankizumab 600 mg (n=206), IV risankizumab 1200 mg (n=205), or placebo (n=207) at weeks 0, 4, and 8. Randomization was stratified by the number of previous biologics, corticosteroid use at baseline and Simple Endoscopic Score for Crohn's Disease (SES-CD). The co-primary endpoints were clinical remis-

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sion and endoscopic response at week 12. Clinical remission was defined as CDAI <150 or as patient-reported outcome symptom criteria including an average daily stool frequency of ≤2.8 and an average daily abdominal pain score ≤1. Endoscopic response was defined as a decrease in SES-CD of >50% or at least a 2-point reduction from baseline for patients with isolated ileal disease and a baseline SES-CD of 4. Significantly higher rates of clinical remission and endoscopic response were achieved in the active treatment groups in both studies. Select results are listed in Table 1. The authors concluded that IV risankizumab was an effective and well-tolerated induction therapy in patients with moderately to severely active CD.

Table 1: Select Results from ADVANCE and MOTIVATE at 12 weeks[9]

	Risankizumab 1200mg IV	Treatment Difference Compared to Placebo	Risankizumab 600mg IV	Treatment Difference Compared to Placebo
ADVANCE				
CDAI Clinical Remission	42%	17% [95% CI 8-25] p<0.0001	45%	21% [95% CI 12-29] p<0.0001
Symptom Clinical Remission	41%	19% [95% CI 11-27] p<0.0001	43%	22% [95% CI 14-30] p<0.0001
Endoscopic Response	32%	20% [95% CI 14-27] p<0.0001	40%	28% [95% CI 21-35] p<0.0001
MOTIVATE				
CDAI Clinical Remission	40%	21% [95% CI 12-29] p<0.0001	42%	22% [95% CI 13-31] p<0.0001
Symptom Clinical Remission	40%	20% [95% CI 12-29] p<0.0001	35%	15% [95% CI 6-24] p=0.0007
Endoscopic Response	34%	23% [95% CI 15-31] p<0.0001	29%	18% [95% CI 10-25] p<0.0001

CDAI=Crohn's disease activity index

The FORTIFY study was a phase III, randomized, double-blind, placebo-controlled trial that evaluated the use of subcutaneous (SUBQ) risankizumab as maintenance therapy for CD.[10] Patients (N=542) who had a clinical response in the ADVANCE and MOTIVATE trials were re-randomized to SUBQ risankizumab 180 mg every 8 weeks (n=179), SUBQ risankizumab 360 mg every 8 weeks (n=179), or placebo (n=184). The co-primary endpoints were the same as the ADVANCE and MOTIVATE trials. In the SUBQ risankizumab 360 mg group at week 52, sustained CDAI clinical remission was observed in 74 (52%) of patients (adjusted treatment difference 15%, 95% CI 4-5), sustained symptom clinical remission was observed in 73 (52%) of patients (adjusted treatment difference 15%, 95% CI 5-25), and sustained endoscopic response was observed in 66 (47%) of patients (adjusted treatment difference 28%, 95% CI 19-37) patients. The 180 mg SUBQ dose did not produce statistically significant results for some of the endpoints and thus is not FDA-approved. The authors concluded that SUBQ risankizumab was safe and effective as maintenance therapy for moderately to severely active CD.

Safety: In the induction trials, the most common side effects were upper respiratory infections (11%), headache (7%), and arthralgia (5%).[9] Serious infections occurred in 5.6% of the treatment group compared to 2.1% in the control group. In the maintenance trial, the most common side effects were arthralgia (9%), abdominal pain (9%), and injection site reactions (6%).[10]

Dosing and Administration: Risankizumab is administered as a 600 mg infusion at weeks 0, 4, and 8 for induction, followed by a maintenance SUBQ dose of 360 mg at week 12 and every 8 weeks thereafter.[7,8] Risankizumab solution is diluted with 5% dextrose and water for a final concentration of 1.2 to 6 mg/mL and infused intravenously over 1 hour. The SUBQ injection may be administered in the thighs, abdomen, or back of upper arms under the supervision of a healthcare professional; self-administration may be allowed after proper training.

Cost and Availability: Risankizumab is available as 600 mg/10 mL single-dose vial NDC 0074-5015-01 (carton of 1) that has an average wholesale price of $10,964 per vial and as a 360 mg/2.4 mL single-dose prefilled cartridge with on-body injector NDC 0074-1070-01 (kit) that has an average wholesale price of $21,927 per injection.[7,8] The average annual cost of therapy will be approximately $142,520.[8]

Formulary Status: Risankizumab is on the CCHS Adult Formulary, restricted to the Department of Gastroenterology for outpatient use only.

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Acetaminophen/ Caffeine (Excedrin® Tension Headache) Tablets	Analgesic	Headache	No restrictions
Capsaicin 8% (Qutenza®) Transdermal Patch	Analgesic	Neuropathic Pain	Restricted to outpatient use only
Levonorgestrel-Releasing Intrauterine System (Liletta®)	Contraceptive	Contraception	Restricted to outpatient use only
Teclistamab (Tecvayli®) Injection	Monoclonal Antibody	Relapsed/Refractory Multiple Myeloma	Restricted to Hematology/ Oncology for treatment of relapsed/refractory multiple myeloma. After the first three doses, it is restricted to out-patient use only.
Tick-Borne Encephalitis Vaccine (TicoVac™)	Vaccine	Prevention of Tick-Borne Encephalitis	Restricted to outpatient use only
Terlipressin (Terlivaz®) Injection	Antidiuretic Hormone Analog	HRS	Restricted to Hepatology and Nephrology in consultation with the Intensivist for adult patients with HRS admitted to the ICU for initiation of therapy and during the first 5 days of therapy*
Tremelimumab (Imjudo®) Injection	Monoclonal Antibody	Hepatocellular Carcinoma	Restricted to Hematology/ Oncology for outpatient use only
Treprostinil Dry Powder Inhalation (Tyvaso DPI™)	Prostaglandin	Pulmonary Arterial Hypertension	Restricted to continuation of home therapy

*Further details regarding terlipressin use is in Lexicomp
HRS=Hepatorenal Syndrome ICU=Intensive care unit

Removals from Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal**
Bebtelovimab and Tixagevimab/ Cilgavimab (Evusheld™)	Monoclonal Antibody	COVID Monoclonal Antibody Treatment and Pre-Exposure Prophylaxis	These agents do not retain activity against the dominant circulating SARS-CoV2 Omicron subvariants.*
Diphtheria and Tetanus Vaccine	Vaccine	Prevention of Diphtheria and Tetanus Infections	Manufacturer discontinued vaccine

*Removal of these agents went into effect 12/1/2022.
COVID=Coronavirus disease 19 SARS-CoV2=Severe acute respiratory syndrome coronavirus 2

Changes to Restrictions of the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions/ Comments**
Cefepime Injection	Antibiotic	Various Infections	Removed all restrictions
Lipid Emulsion (fish oil and plant based) (SMOFlipid®) Injection	Caloric Agent	Parenteral Nutrition	Removed all restrictions
Lymphocyte Immune Globulin (ATGAM®) Injection	Immune Globulin	Various Indications	Modify restriction to: 1) Hematology/Oncology and BMT 2) Transplant Services for patients who are unable to tolerate anti-thymocyte globulin (rabbit) (Thymoglobulin®)
Rituximab (Ruxience®) Injection	Monoclonal Antibody	Various Indications	Modify restriction to state: Restricted to Transplant Staff Physicians for the treatment of antibody-mediated rejection with allograft dysfunction. For treatment of post-transplant PTLD, **a Hematology/Oncology provider must place the order in Epic.**
Ulipristal (Ella®)	Contraceptive	Emergency Contraception	Removed all restrictions

BMT=Bone marrow transplant PTLD=Post-transplant lymphoproliferative disease

Process Changes to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Dose Rounding Details**
Ketamine (Ketalar®) Injection	General Anesthetic	Analgesia/Sedation	Pharmacists may round the ketamine bolus doses to the nearest 5 mg. Doses <2.5 mg round down Doses ≥2.5 mg round up
Methylene Blue Injection	Antidote	Various Indications	Pharmacists may round the methylene blue doses to the nearest 50 mg ampule of medication. Doses < 25 mg round down Doses ≥ 25 mg round up

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Calaspargase Pegol (Asparlas™) Injection	Enzyme	ALL	Restricted to the Department of Pediatric Hematology/Oncology
N-acetylcysteine Capsules	Antidote Mucolytic Agent	Polysubstance Abuse Disorders Marijuana Cravings	No restrictions
Tick-Borne Encephalitis Vaccine (TicoVac™)	Vaccine	Prevention of Tick-Borne Encephalitis	Restricted to outpatient use only

ALL=Acute lymphoblastic leukemia

Changes to Restrictions of the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes**
Bortezomib (Velcade®)	Antineoplastic Agent	Pre-transplant Desensitization	Restricted to Staff Physicians from the Department of Transplant for the treatment of pre-transplant desensitization.
Rituximab (Rituxan®)	Monoclonal Antibody	Pre-transplant Desensitization	Restricted to Staff Physicians from the Department of Transplant for the treatment of pre-transplant desensitization.
Ulipristal (Ella®)	Contraceptive	Emergency Contraception	Removed all restrictions

Removal from the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal**
Diphtheria and Tetanus Vaccine	Vaccine	Prevention of Diphtheria and Tetanus Infections	Manufacturer discontinued vaccine

Process Changes to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Dose Rounding Details**
Insulin Lispro (Admelog®)	Insulin	Diabetes	Pharmacists may round doses as follows: **For doses 0-9.9 units** round to the nearest 0.5 unit (e.g., dose 3.4 units would round to 3.5 units) **For doses ≥ 10 units** round to the nearest 1 unit (e.g., dose 11.8 units would round to 12 units)
Insulin Glargine (Lantus®)	Insulin	Diabetes	Pharmacists may round doses as follows: **For doses 0-9.9 units** round to the nearest 0.5 unit (e.g., dose 3.4 units would round to 3.5 units **For doses ≥ 10 units** round to the nearest 1 unit (e.g., dose 11.8 units would round to 12 units)