Cleveland Clinic Clinical Rx Forum

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Rituximab Biosimilar for Rheumatoid Arthritis

By: Nicole Babiak, Pharm.D.

Background: Rituximab (Rituxan®; Genentech) is approved by the Food and Drug Administration (FDA) for a variety of indications including rheumatoid arthritis (RA).[1] There are currently two rituximab biosimilars approved by the FDA: rituximab-pvvr (Ruxience®; Pfizer) and rituximab-abbs (Truxima®; Teva).[2,3] Biosimilars, although not identical to their reference biologics, are very similar in safety, purity, and potency.[4] Additionally, like generic medications, biosimilar products are less costly than their corresponding brand-name products making them more accessible. For a biosimilar to be approved, an abbreviated application [351(k)] must be completed, which demonstrates similarities to the reference product in pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, safety, and efficacy. Only one efficacy trial for a single FDA-approved indication is required for approval of a biosimilar agent since data from this trial can be extrapolated to other indications. In the case of Ruxience®, the efficacy trial submitted to the FDA was to support its use in rheumatoid arthritis (RA). Table 1 displays the FDA-approved indications for Rituxan®, Ruxience®, and Truxima®. It is important to note that Pfizer decided not to pursue a labeled indication of RA for Ruxience® even though the studies that helped gain its FDA approval evaluated its use for that specific indication.[5] Rheumatoid arthritis is a chronic inflammatory disease that results in articular cartilage and bone destruction.[6] Initial treatment for RA includes disease-modifying anti-rheumatic drugs (DMARDs) with methotrexate or tumor necrosis factor (TNF) antagonists for patients with an inadequate response to DMARDs. Patients refractory to TNF antagonists are recommended to begin rituximab with a stable dose of methotrexate.

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Ruxolitinib for Steroid-Refractory Graft-Versus-Host Disease

By: Sonya Anderson, Pharm.D.

Background: In patients with hematologic malignancies and non-malignant hematologic diseases, allogeneic hematopoietic stem cell transplantation (allo-HSCT) presents a potentially curative treatment option.[1] However, allo-HSCT is not without risk. Acute graft-versus-host disease (GVHD) is a life-threatening complication following allo-HSCT. Through an immunologically mediated process, allo-reactive donor T cells lead to the dysregulation of inflammatory cytokine cascades.[2] End-organ tissue damage to the gastrointestinal tract, liver, and skin are major causes of morbidity and mortality in allo-HSCT recipients.[3] Despite prophylaxis with immunomodulatory agents, acute GVHD occurs in 30-50% of allo-HSCT recipients.[4] Steroids remain the mainstay of first-line management.[5] However, many patients do not experience sustained responses. When steroids failed, there was no true standard second-line agent until ruxolitinib (Jakafi®; Incyte Corporation) was approved by the Food and Drug Admin-

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Table 1: FDA-Approved Indications for Rituximab Products [1-3]

Indications	Rituxan® (Reference drug) Rituximab	Ruxience® (Rituixmab-pvvr)	Truxima® (Rituximab-abbs)
Non-Hodgkin's Lymphoma	X	X	X
Chronic Lymphocytic Leukemia	X	X	X
Rheumatoid Arthritis	X		X
Granulomatosis with Polyangiitis and Microscopic Polyangiitis	X	X	X
Pediatric Granulomatosis with Polyangiitis and Microscopic Polyangiitis	X		
Pemphigus Vulgaris	X		

FDA=Food and Drug Administration

Mechanism of Action: B cells play a key role in the pathogenesis of RA.[4] Rituximab, a chimeric IgG1/k monoclonal antibody, acts as a CD20 antagonist, which causes B cell lysis and depletion.

Key Clinical Trial: Ruxience® was evaluated in a phase 1, double-blind, randomized, parallel, three-arm PK trial.[4] Two-hundred and twenty patients with active RA met inclusion criteria, with 198 patients meeting per-protocol requirements. Patients received either 1000 mg of Ruxience® (n=68), rituximab-EU (European rituximab; TherMab®)(n=67), or rituximab-US (United States rituximab-Rituxan®) (n=63) on day 1 and day 15. Results showed similarities among groups in PK, PD, safety, and immunogenicity. An extension study was completed that allowed for continued treatment and further evaluation of those parameters after the transition from the rituximab reference product to Ruxience®.[7] As part of this study, patients completed up to a total of three courses of therapy. In the first course, 185 patients were assigned treatment as follows: those who received Ruxience® in the parent trial continued with this therapy, those who had received rituximab-EU or rituximab-US were randomized 1:1 to either continue with the previously assigned therapy or to receive Ruxience®. Doses were administered on days 1 and 15 separated from the next dosing regimen by 24 weeks (±8 weeks). For courses two and three, all patients received Ruxience®. Only descriptive statistics were used since the study was not designed for inferential statistics. Demographics were similar among all treatment groups. Like the parent study, there were no notable differences in drug concentrations, B cell depletion levels or other pharmacologic parameters between treatment arms. The overall remission rate at the end of treatment was similar between groups at approximately 36.6%.

Safety and Immunogenicity: The most frequently occurring adverse effects (AEs) in the extension trial were infections and worsening of RA.[7] Common AEs (occurring in >10%) included fever, lymphopenia, asthenia, neutropenia, cardiovascular effects, nausea, diarrhea, peripheral edema, and headache. Infusion-related reactions were observed in 3.7% and anti-drug antibodies occurred in 12%.

Dosing and Administration: The recommended dose of rituximab for RA is two 1000 mg intravenous infusions, separated by 2 weeks.[1-3] This dosage regimen is repeated every 24 weeks (or based on clinical evaluation), but no sooner than every 16 weeks.

Cost and Availability: Ruxience® is available as a 100 mg/10 mL and 500 mg/50 mL solution in single-dose vials with an average wholesale price of $86.02 per mL.[8] Rituxan® is available as a 100 mg/10 mL and 500 mg/50 mL solution in single-dose vials with an average wholesale price of $112.74 per mL. The annual cost for a patient receiving Ruxience® is approximately $17,204. The annual cost for a patient receiving Rituxan® is approximately $22,548. This is a $5344 cost difference per patient on an annual basis.

Formulary Status: The Cleveland Clinic Health-System will be utilizing Ruxience® as its preferred rituximab biosimilar.

References:

1. Rituxan® [package insert]. South San Francisco, CA: Genentech, Inc.; Sept 2019.
2. Ruxience® (rituximab-pvvr) [package insert]. New York, NY: Pfizer Labs; May 2020.
3. Truxima® (rituximab-abbs) [package insert]. North Wales, PA: Teva Pharmaceuticals; March 2020.
4. Cohen S, Emery P, Greenwald M, Yin D, Becker JC, Li R, et al. A phase I pharmacokinetics trial comparing PF-05280586 (a potential biosimilar) and rituximab in patients with active rheumatoid arthritis. Br J Clin Pharmacol. 2016;82(1):129-38.
5. Rituxan® [product information]. South San Francisco, CA: Genentech, Inc.; July 2020.
6. Singh JA, Saag KG, Bridges Jr. SL, Akl EA, Bannuru RR, Sullivan MC et al. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Care Res. 2016;68(1):1-25.
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8. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp Inc.; 2020: August 3, 2020.

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istration in May 2019 for the treatment of steroid-refractory acute GVHD in adult and pediatric patients ≥12 years of age.[6]

Mechanism of Action: Janus kinases (JAKs) are enzymes involved in recruiting signal transducers and activators of transcription (STATs) to cytokine receptors.[6] Ruxolitinib inhibits the JAK-STATS pathway, which plays an important role in the development, proliferation, and activation of immune cells involved in GVHD pathogenesis.

Clinical Trials: The safety and efficacy of ruxolitinib were evaluated in two clinical trials, REACH1 and REACH2.[7,8] REACH1 was a prospective, multicenter, open-label, single-cohort, phase 2 trial that enrolled patients ≥ 12 years of age with grade II–IV steroid-refractory GVHD who had received no more than one systemic treatment in addition to corticosteroids.[7] Patients (n=71) received ruxolitinib 5 mg twice daily, with an option to increase to 10 mg twice daily after 3 days in the absence of cytopenias. The primary outcome was overall response rate (ORR) at day 28. The ORR at day 28 was 54.9%, with 26.8% achieving a complete response, 9.9% a very good partial response, and 18.3% a partial response. The median overall survival was 7.6 months. Approximately 55.8% of those receiving ruxolitinib had ≥ 50% reduction of corticosteroid use from baseline. The authors concluded that ruxolitinib was an effective treatment option for steroid refractory acute GVHD and was associated with improved survival. REACH2 was a prospective, multicenter, open-label, randomized, phase 3 trial that enrolled the same patient population as REACH1.[8] Patients (n=309) were randomized to receive ruxolitinib 10 mg twice daily (n=154) or the investigator's choice of nine different treatments (e.g., extracorporeal photopheresis, mycophenolate, etanercept) (n=155) for up to 24 weeks. Extracorporeal photopheresis (27%) was the most common initial therapy in the control group. The primary outcome was ORR on day 28. The ORR on day 28 was significantly higher in the ruxolitinib group than the control group (62% vs. 39%, respectively, P< 0.001), with 34% and 19% of those patients achieving a complete response, respectively. Median overall survival was 11.1 months in the ruxolitinib group compared to 6.5 months in the control group (HR: 0.83; 95% CI, 0.60-1.15). Thrombocytopenia occurred in 33% of those treated with ruxolitinib who had any grade of GVHD compared to 18% of the corresponding control group. The authors concluded that ruxolitinib treatment resulted in a significantly higher ORR than other second-line therapies but with a higher thrombocytopenia rate.

Safety: Common adverse effects (occurring in >15% of the treatment group) included anemia, thrombocytopenia, neutropenia, infections, edema, hemorrhage, elevated alanine aminotransferase and aspartate aminotransferase, fatigue, dyspnea, thrombosis, diarrhea, rash, headache, hypertension, and dizziness.[6] Lipid elevations and non-melanoma skin cancer were also associated with ruxolitinib use.

Dosing and Administration: The recommended starting dose of ruxolitinib for the treatment of GVHD is 5 mg given orally twice daily.[6] The dose may be increased to 10 mg twice daily after at least 3 days if the absolute neutrophil count (ANC) and platelet count are not decreased by ≥50% relative to the first day of treatment. If a dose is missed, it is recommended to skip the missed dose and then resume the regular dosing schedule. Ruxolitinib may be tapered after 6 months in patients who respond and have discontinued therapeutic doses of corticosteroids. There are dosage adjustments based on various clinical factors (e.g., total bilirubin elevations, ANC levels, thrombocytopenia, use of strong cytochrome P450 3A4 inhibitors, renal/hepatic impairment) listed in the package insert. Ruxolitinib tablets can be suspended in 40 mL of water after stirring for 10 minutes and administered through a nasogastric tube within 6 hours of preparation.

Cost and Availability: Ruxolitinib is available as 5 mg and 10 mg tablets.[6,9] The average wholesale price of a tablet is about $275. The estimated annual cost of therapy is $201,100.

Formulary Status: Ruxolitinib was added to the CCHS Pediatric Formulary restricted to the Department of Pediatric BMT for use in patients with steroid-refractory acute or chronic GVHD.

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1. Blazar BR, Murphy WJ, Abedi M. Advances in graft-versus-host disease biology and therapy. Nat Rev Immunol. 2012;12(6):443-58.
2. Henden AS, Hill GR. Cytokines in graft-versus-host disease. J Immunol. 2015;194(10):4604-12.
3. Nassereddine S, Rafei H, Elbahesh E, Tabbara I. Acute graft versus host disease: a comprehensive review. Anticancer Res. 2017;37:1547-55.
4. Zeiser R, Blazar BR. Acute graft-versus-host disease – biologic process, prevention, and therapy. N Engl J Med. 2017;377:2167-79.
5. Garnett C, Apperley JF, Pavlu J. Treatment and management of graft-versus-host disease: improving response and survival. Ther Adv Hematol. 2013;4(6):366-78.
6. Jakafi [package insert]. Wilmington, DE: Incyte Corporation; May 2019.
7. Jagasia M, Perales MA, Schroeder MA, Ali H, Shah NN, Chen YB, et al. Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label phase 2 trial. Blood. 2020;135 (20):1739-49.
8. Zeiser R, von Bubnoff N, Bulter J, Mohty M, Niderwiser D, Or R, et al. Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. N Engl J Med. 2020;382:1800-10.
9. Lexi-Comp Online, Lexi-Drugs Online, Ohio Lexi-Comp Inc, August 3, 2020.

Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Belantamab mafodotin (Blenrep®)	Monoclonal Antibody	Multiple Myeloma (Relapsed/Refractory)	Restricted to the Department of Hematology and Medical Oncology for outpatient use only for on-label indication
Brexpiprazole (Rexulti®)	Atypical Antipsychotic	MDD Schizophrenia	Restricted to the Department of Psychiatry for initiation of therapy. There are no restrictions for continuation of home therapy
Brexucabtagene autoleucel (Tecartus®)	CAR-T Cell Immunotherapy	Mantle Cell Lymphoma (Relapsed/Refractory)	Restricted to the Department of Hematology/ Oncology and Bone Marrow Transplantation
Cariprazine (Vraylar®)	Atypical Antipsychotic	MDD Schizophrenia Bipolar Disorder	Restricted to the Department of Psychiatry for initiation of therapy. There are no restrictions for continuation of home therapy
Cefiderocol (Fetroja®)	Antibiotic	Documented or suspected carbapenem-resistant gram-negative bacteria	Restricted to Infectious Diseases Physicians for the treatment of documented or suspected carbapenem-resistant Gram-negative bacteria
Ceftazidime (Fortaz®)	Antibiotic	Various infections	Restricted to the Department of Infectious Diseases
Dexamethasone ophthalmic insert (Dextenza®)	Corticosteroid	Treatment of ocular inflammation and pain following ophthalmic surgery	Restricted to the Department of Ophthalmology for outpatient use only in Medicare patients
Diltiazem IV bolus	Calcium Channel Blocker	Various cardiac indications	No restrictions
Fostemsavir (Rukobia™)	Antiretroviral Agent	HIV infection	No restrictions
Inebilizumab (Uplizna®)	Monoclonal Antibody	NMOSD	Restricted to the Department of Neurology for on-label indication (treatment of NMOSD in adults who are AQP4antibody positive) for outpatient use only
Intralesional Bleomycin	Antineoplastic Agent	Refractory warts	Restricted to the Department of Dermatology for outpatient use only
Orphenadrine Injection (Norflex®)	Skeletal Muscle Relaxant	Muscle Spams	Restricted to patients refractory to or unable to take an oral/enteral skeletal muscle relaxant
Preservative-free Nicardipine Injection	Calcium Channel Blocker	Blood pressure management associated with ICH or SH	Reserved for IVT/IT route of administration only

MDD=Major depressive disorder IV=Intravenous HIV=Human immunodeficiency virus
NMOSD=Neuromyelitis optica spectrum disorder AQP4=Anti-aquaporin-4 ICH=Intracranial hemorrhage
SH=Subarachnoid hemorrhage IVT=Intraventricular IT=Intrathecal

Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Tafasitamab (Monjuvi®)	Monoclonal Antibody	Diffuse B Cell Lymphoma (Refractory/Relapsed)	Restricted to Department of Hematology/Oncology for outpatient use only
Velaglucerase (Vpriv®)	Enzyme	Gaucher's Disease	Restricted to the Department of Hematology/Oncology for outpatient use only*
Vilazodone (Viibryd®)	Antidepressant	MDD	Restricted to the Department of Psychiatry for initiation of therapy There are no restrictions for continuation of home therapy.
Vortioextine (Trintellix®)	Antidepressant	MDD	Restricted to the Department of Psychiatry for initiation of therapy There are no restrictions for continuation of home therapy.

MDD=Major depressive disorder
*Note: Needs to be on the CCHS Formulary due to some insurance companies mandating use over current Formulary agents.

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Avelumab (Bavencio®)	Monoclonal Antibody	Various Cancers	Restricted to Hematology/ Oncology for outpatient use only*
Bivalirudin (Angiomax®)	Anticoagulant	Alternative anticoagulant in patients with HIT	Modified restrictions to include restricted to Vascular Surgery for patients with HIT for emergent surgery
Carisoprodol (Soma®)	Skeletal Muscle Relaxant	Muscle Spasm	Restricted to continuation of home therapy
Imipenem/Cilastatin (Primaxin®)	Antibiotic	Various Infections	Modified restrictions to include the Department of Infectious Diseases for the treatment of meropenem-resistant *Pseudomonas spp*.
Rituximab (Rituxan®)	Monoclonal Antibody	Various Indications	Modified restrictions to include highly sensitized intestinal transplant patients (DSA >4000 MFI) for induction with continued monitoring per protocol with regards to infection and rejection

HIT=Heparin-induced thrombocytopenia DSA=Donor-specific antibodies MFI=Mean fluorescent intensity
*Note: We are removing the specific indications from the restriction; avelumab should be used for on-label indications.

Removals from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal**
Ampicillin (Oral)	Antibiotic	Various Infections	Removed since ampicillin oral suspension has been withdrawn from the market and oral amoxicillin can be used in place of ampicillin capsules due to similar anti-microbial coverage and side effect profile
Chloroxazone (Parafon Forte® DSC)	Skeletal Muscle Relaxant	Muscle spasm	Removed due to low use
Metaxalone (Skelaxin®)	Skeletal Muscle Relaxant	Muscle spasm	Removed from CCHS Adult Formulary as part of oral skeletal muscle relaxant standarization
Oral magnesium supplements: magnesium chloride (SLO-MAG) magnesium gluconate (MAG-G) magnesium oxide (URO-MAG)	Electrolyte	Hypomagnesemia	Removed from the CCHS Adult Formulary as part of the oral magnesium supple-ment standardization
Orphenadrine ER (Norflex®) tablets	Skeletal Muscle Relaxant	Muscle spasm	Removed from the CCHS Adult Formulary as part of the oral skeletal muscle relax-ant standardization
Ribavirin, inhaled (Virazole™)	Antiviral Agent	RCV Infection	Removed due to low use and increase in cost
Tizanidine (Zanaflex®) capsules	Alpha adrenergic Agonist	Muscle spasm	Removed as part of the oral skeletal muscle relaxant standardization initiative. Tizanidine tablets which are a lower cost will remain on Formulary
Sodium Chloride 2% bolus	Electrolyte	Hyponatremia	Removed to encourage use of 3% sodium chloride boluses and to minimize delays in ad-ministration due to prepara-tion

RCV=Respiratory syncytial virus

Product Standardizations of the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Standardization**
Ampicillin (Oral)	Antibiotic	Various Infections	A therapeutic interchange from oral ampicillin to oral amoxicillin was approved.*
Amoxicillin/ clavulanate (Augmentin®)	Antibiotic	Various Infections	Amoxicillin/clavulanate suspension 400 mg/57 mg/5mL will be used for a dose of 880 mg/125.4 mg/11 mL as a conversion from amoxicillin/ clavulanate 875 mg/125mg tablet dose.
Diltiazem Extended-Release Tablets/Capsules	Calcium Channel Blocker	Various Cardiac Indications	A therapeutic interchange for all diltiazem extended-release products was approved.*
Magnesium Oral supplements	Electrolyte	Hypomagnesemia	A therapeutic interchange for oral magnesium supplements was approved.
Oral Skeletal Muscle Relaxants	Skeletal Muscle Relaxant	Muscle spasm	A therapeutic interchange for oral skeletal muscle relaxants was approved.*

*Details in Lexicomp

Process Changes of the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Process Change**
Ampicillin (Oral)	Antibiotic	Various Infections	Updated renal dosing context*
C-1 esterase Inhibitor (Cinryze®)	C-1 esterase inhibitor	Angioedema (various)	Pharmacists may automatically round Cinryze® to the nearest 500 units (500 units/ vial). If <250 units, pharmacist to round down; if ≥ 250 units, pharmacist to round up
Desmopressin (DDAVP) Injection	Hormone	Diabetes Insipidus	Weight-based dosing*†
Inhalers	Various Pharmacologic Classes	Various Indications	Inhalers used for patients who are non-mechanically ventilated , outside of the ED, or not under Observation status Nebulizers used for patients who are mechanically ventilated, in the ED, or under Observation status‡

ED=Emergency department
*Available in Epic
†Weight based doses will be automatically rounded to the nearest 4 mcg
‡This interchange will not impact the nebulizer to inhaler therapeutic interchange for COVID-19 patients and persons under investigation for COVID-19.

Denials to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Denial**
Lurbinectedin (Zepzelca®)	Antineoplastic Agent	Metastatic small cell lung cancer	Due to lack of robust evidence comparing this agent to current second-line standard-of-care topotecan
Trastuzumab and hyaluronidase (Herceptin Hylecta®)	Monoclonal Antibody	HER2-overexpressing breast cancer	Due to the significantly higher cost of this agent compared to IV trastuzumab biosimilar
Trastuzumab, pertuzumab and hyaluronidase (Phesgo®)	Monoclonal Antibody	HER2-positive early breast cancer	Due to non-inferiority and a higher cost compared to IV trastuzumab biosimilar plus IV pertuzumab

HER2=Hormone estrogen receptor 2 IV=Intravenous

Product Standardization to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Denial**
Amoxicillin/ clavulanate (Augmentin®)	Antibiotic	Various Infections	See Adult Formulary section

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Fostemsavir (Rukobia™)	Antiviral Agent	HIV Infection	No restrictions
Cefiderocol (Fetroja®)	Antibiotic	Documented or suspected carbapenem-resistant gram-negative bacteria	Restricted to Pediatric Infectious Diseases for the treatment of documented or suspected carbapenem-resistant Gram-negative bacteria
Ceftazidime (Fortaz®)	Antibiotic	Various infections	Restricted to the Pediatric Infectious Diseases
Mifepristone (Mifeprex®)	Progestin Antagonist	Management of miscarriages	Restricted to Obstetrics/ Gynecology providers who are REMS certified
Peanut allergen Powder-dnfp (Palforzia™)	Immunotherapy	Peanut Allergy	Restricted to Allergy and Clinical Immunology providers certified with the Palforzia™ REMS Program for outpatient use only Continuation of Palforzia™ therapy from home during an inpatient admission requires an Allergy and Clinical Immunology consult
Ruxolitinib (Jakafi®)	JAK inhibitor	Steroid-refractory GVHD	Restricted to the Department of Pediatric BMT for use in patients with steroid-refractory acute or chronic GVHD

HIV=Human immunodeficiency virus REMS=Risk evaluation mitigation strategy JAK=Janus kinase
GVHD=Graft-versus-host disease BMT=Bone marrow transplant

Removals from the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Denial**
Ampicillin (Oral)	Antibiotic	Various Infections	See Adult Formulary section
Ribavirin, inhaled (Virazole™)	Antiviral Agent	RCV Infection	See Adult Formulary section
Sodium Chloride 2% bolus	Electrolyte	Hyponatremia	See Adult Formulary section

RCV=Respiratory syncytial virus

Changes in Restrictions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Anakinra (Kineret®)	Antirheumatic	MIS-C	Modified restrictions to include the Department of Pediatric Rheumatology for the management of MIS-C
Cefepime (Maxipime®)	Antibiotic	Various Infections	Removed all restrictions
Goserelin (Zoladex®)	GRH Agonist	Fertility Preservation	Added restriction as follows: Restricted to the Department of Pediatric Hematology/ Oncology for fertility preservation
Imipenem/cilastatin (Primaxin®)	Antibiotic	Meropenem-resistant *Pseudomonas spp.* Infections	Modified restrictions to include Pediatric Infectious Diseases for the treatment of meropenem-resistant *Pseudomonas spp.*
Infliximab (Remicade®)	Monoclonal Antibody	Kawaski Disease Anakinra-refractory MIS-C	Modified restrictions to include: 1. The Department of Pediatric Rheumatology for the management of anakinra-refractory MIS-C 2. The Department of Pediatric Rheumatology for the management of Kawaski Disease
Leuprolide (Lupron®)	GRH-Agonist	Fertility Preservation	Modified restriction to include: Leuprolide Acetate Depot (Lupron® Depot and Lupron® Depot-PEDS) injection inpatient use is restricted to Pediatric Hematology/ Oncology for fertility preservation
Levetiracetam (Keppra®) Injection	Anticonvulsant	Various Seizures	Modified restrictions so that use in acute seizures or suspected or confirmed status epilepticus is no longer restricted
Romiplostim (Nplate®)	CSF	Various Thrombocytopenias	Modified restrictions to the Department of Pediatric Hematology/Oncology and BMT
Tocilizumab (Actemra®)	Monoclonal Antibody	Anakinra-refractory MIS-C	Modified restrictions to include the Department of Pediatric Rheumatology for the management of anakinra-refractory MIS-C

MIS-C=Multisystem inflammatory syndrome in children GRH=Gonadotropin-releasing hormone
CSF=Colony stimulating factor BMT=Bone marrow transplant