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Adzynma™ for Congenital Thrombotic Thrombocytopenic Purpura

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What is congenital thrombotic thrombocytopenic purpura? Congenital thrombotic thrombocytopenic purpura (cTTP) is a rare genetic disorder associated with mutations within the ADAMTS13 gene leading to a chronic deficiency of the ADAMTS13 enzyme.[1-4] The ADAMTS13 enzyme cleaves von Willebrand factor (vWF) multimers, and deficiency in this enzyme results in unusually large vWF multimers that attract platelet aggregation leading to thrombi formation in small vessels. Within TTP, cTTP represents a small minority of cases (≤5%). Congenital TTP is diagnosed based on documentation of ADAMTS13 deficiency (ADAMTS13 activity of <10%), an absence of ADAMTS13 autoantibody inhibitors, and confirmation of ADAMTS13 mutations.

What are the current treatments for cTTP and, how do they compare? The mainstay of therapy for cTTP has been the replacement of the absent or deficient ADAMTS13 enzyme utilizing fresh frozen plasma (FFP) infusions.[2,4] Treatment can be given on demand (during acute episodes only) or prophylactically on a scheduled basis. For a 70 kg patient the dose of FFP would be 10 to 15 mL/kg requiring an infusion volume of 700 to 1050 mL, which would take approximately 2 to 4 hours to administer.[3] Potential disadvantages of FFP include fluid overload due to excessive volume, transfusion-related acute lung injury, allergic or anaphylactic reactions, long infusion time, inconvenience of frequent infusion site visits, and potential risk of bloodborne infection.[2] Adzynma™ is a new treatment for cTTP. Unlike human plasma products, which carry a risk of bloodborne infection, Adzynma™ is produced in a plasma protein-free milieu and does not use additives of human or animal origin in its cell culture and purification processes. The volume for a dose of Adzynma™ compared with FFP is substantially less, allowing for a much shorter infusion time. For a 70 kg patient requiring a 40 IU/kg dose of Adzynma™ the volume would be about 10 mL which could be infused over 2.5 to 5 minutes.

What is the mechanism of action of Adzynma™? Adzynma™ is a recombinant form of the endogenous ADAMTS13 enzyme.[5] ADAMTS13 is a plasma zinc metalloprotease that regulates the activity of vWF by cleaving large and ultra-large vWF multimers to smaller units, thereby reducing the platelet binding properties of vWF and its propensity to form microthrombi.

What literature supports the use of Adzynma™ in cTTP? Jain and colleagues performed a phase 3 randomized, active-controlled, open-label, two-period crossover study followed by a single-arm continuation trial to evaluate the safety and efficacy of Adzynma™.[2,5-6] This multi-center trial compared the prophylactic and on-demand treatment of Adzynma™ to the standard of care (SoC) in patients with cTTP. Pa-

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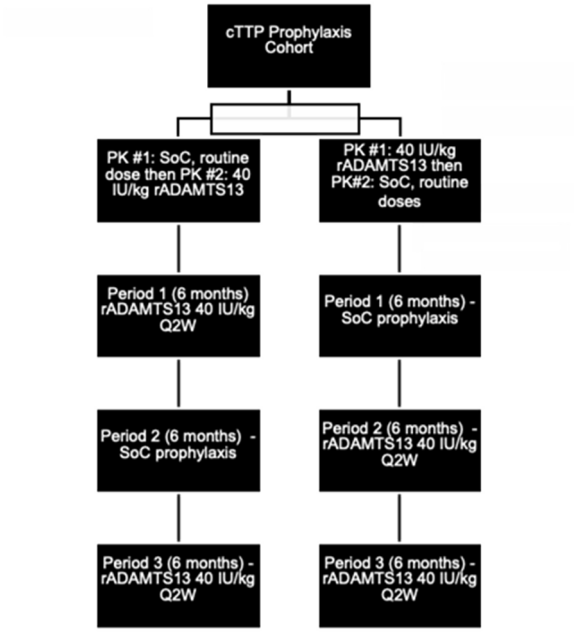
tients were initially randomized to either SoC or Adzynma™, then after 14 ± 2 days, there was a crossover to the opposite therapy. After the second crossover, the patients were maintained on the same therapy assessed for 6 months (Period 1), then crossed over to the other therapy (Period 2) for another 6 months. After Period 2, all patients were placed on Adzynma™ 40 IU/kg every 2 weeks until study completion in 6 months (Period 3) with the opportunity to enroll in an open-label continuation study. Figure 1 details the study design alongside period times and therapies of this phase 3 study.

Figure 1: Phase 3 Study Design[2]



Interim analysis results included data from 48 patients randomized in the prophylaxis group cohort to Adzynma™ or SoC during Period 1 and then crossing over to the alternative treatment for Period 2. The primary outcome measure was the number of acute TTP episodes in patients receiving either SoC or Adzynma™ in the prophylaxis cohort. No patients receiving Adzynma™ had an acute TTP event throughout the study, including in Period 3. One acute TTP event occurred in a patient receiving FFP in Period 1.

What are the common side effects of Adzynma™? The most common adverse reactions (>5% of subjects) reported in clinical trials were headache, diarrhea, migraine, abdominal pain, nausea, upper respiratory tract infection, dizziness, and vomiting.[5] No neutralizing antibodies were detected in any patient in the clinical trial.[2,6]

What are the dosing and administration recommendations for Adzynma™? The prophylactic dosing of Adzynma™ is 40 IU/kg once every other week intravenously.[5] The on-demand therapy dosing is 40 IU/kg body weight on day 1, 20 IU/kg on day 2, and 15 IU/kg on days 3 and beyond until 2 days after the acute event has resolved. Each vial of Adzynma™ must be reconstituted with 5 mL of sterile water before use. Adzynma™ is available as approximate potencies and requires weight-based dosing; therefore, pharmacists can round the dose ± 10% to correspond to the nearest vial size, similar to the dosing of blood factors. Adzynma™ can be administered at home or in a healthcare setting and infused at a rate of 2 to 4 mL/minute.[5] No filter is needed for administration.

What is the cost and availability of Adzynma™? Adzynma™ is packaged as a 500 IU/vial (500 IU vial (NDC: 64764-130-01) and a 1500 IU vial (NDC: 64764-135-01) and costs $3.28 per IU.[5,7] Potency ranges for Adzynma™ are depicted in Table 1. Prophylactic annual therapy for a 70 kg patient costs approximately $240,000.[7] The corresponding cost for FFP would be about $4000.

Table 1: Adzynma™ Dry Powder Potency Ranges[8]

Vial Size	Dry Powder Potency Range
Adzynma™ 500 IU/vial	400-650 IU/vial
Adzynma™ 1500 IU/vial	1200-1950 IU/vial

What is the formulary status of Adzynma™? Adzynma™ was added to the CCHS Adult Formulary restricted to the Department of Hematology and Oncology for congenital thrombotic thrombocytopenic purpura (cTTP) for outpatient use only.

References:

1. George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med. 2014;371(7):654-66.
2. Adzynma™. Dossier. Takeda Pharmaceutical. 2023.
3. George JN, Cuker A. Hereditary thrombotic thrombocytopenic purpura (hTTP). UpToDate Available at: https://www.uptodate.com. Accessed: February 2024.
4. Karsenty CL, Kirk SE, Helber HL, Esquilin JM, Despotovic JM, Grimes AB. Molecular diagnosis is vital to the accurate classification and management of thrombotic thrombocytopenic purpura in children. Front Immunol. 2022; 13:836960.
5. Adzynma™ [package insert]. Lexington, MA: Takeda Pharmaceuticals, Inc.; November 2023.
6. Clinicaltrials.gov [Website]. National Institutes of Health. Bethesda (MD): National Library of Medicine. Available at: https://www.clinicaltrials.gov/search?term=NCT03393975. Accessed: January 2024.
7. Email communication from Lisa Yatsko, Category Manager, Pharmacy Supply Chain Management. January 18, 2024.
8. Email communication from Narinder Kaur, Medical Information Department at Takeda Pharmaceuticals, Inc. February 14, 2023.

Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Avacincaptad Pegol (Izervay™) Intravitreal Injection	Complement Inhibitor	Geographic Atrophy	Restricted to the Department of Ophthalmology for outpatient use only
Chikungunya Vaccine (Ixchiq®) Injection	Live Attenuated Vaccine	Prevention of Chikungunya Infection	Restricted to outpatient use only
Formaldehyde Topical Solution	Hemostatic Agent	Hemorrhagic Radiation Proctitis Hemorrhagic Radiation Cystitis	Restricted to Staff Physicians from the Departments of Colorectal Surgery and Urology
Lifileucel (Amtagvi™) Intravenous Infusion	Cellular Immunotherapy	Unresectable or Metastatic Melanoma	Restricted to the Department of Hematology/Oncology and Bone Marrow Transplantation at Cleveland Clinic Main Campus only
Motixafortide (Aphexda®) Subcutaneous Injection	Hematopoietic Stem Cell Mobilizer	Hematopoietic Stem Cell Mobilization	Restricted to the Department of Hematology/Oncology and Bone Marrow Transplantation for patients with multiple myeloma undergoing hematopoietic stem cell mobilization for autologous transplantation who have failed a prior mobilization attempt with plerixafor
Pimavanserin (Nuplazid®) Oral Capsule	Second Generation Antipsychotic	PDP	Restricted to continuation of home pimavanserin use only
Secukinumab (Cosentyx®) Intravenous Infusion	Monoclonal Antibody	PsA AS nr-axSpA	Restricted to the Department of Rheumatology for the approved indications of PsA, AS, and nr-axSpA for adult outpatient use only Note: Secukinumab subcutaneous injection will remain non-formulary.
Smallpox and Monkeypox Vaccine (Jynneos®) Injection	Live Vaccine	Prevention of Smallpox and Monkey Pox	No Restrictions
Tarlatamab-dlle (Imdelltra®) Intravenous Infusion	Monoclonal Antibody	ES-SCLC	Restricted to the Department of Hematology/Oncology for outpatient use only Inpatient use is restricted to the Department of Hematology/Oncology at Main Campus and Weston only for the first cycle of therapy.

PDP=Parkinson's disease psychosis PsA=Psoriatic arthritis AS=Ankylosing spondylitis nr-axSpA= non-radiographic axial spondylarthritis
ES-SCLC=Extensive stage-small cell lung cancer

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions/ Comments**
Albumin 5% Intravenous Injection	Plasma Volume Expander	Various Indications	Modify restrictions for SICU only: Prescribing of albumin 5% and 25% will be restricted to SICU Medical Staff, SICU Mid-Level Practitioners, SICU Fellows, and PGY3 and PGY4 anesthesia residents rotating in the SICU. These restriction criteria will NOT apply to Medical or Neuro ICU patients boarding in the SICU. A link to the list of approved prescribers is in Lexicomp.
Brentuximab Vedotin (Adcetris®) Intravenous Infusion	Monoclonal Antibody	CD30+PTCL	Modify restrictions to include the Department of Hematology/ Oncology for inpatient use in newly diagnosed CD30+PTCL patients who cannot be discharged due to disease burden.
Ferric Carboxymaltose (Injectafer®) Intravenous Infusion	Iron Supplement	Iron Deficiency	Modify restrictions to include the Department of Cardiology for use in the outpatient setting.
Levonorgestrel Intrauterine Device	Contraceptive	Heavy Intrauterine Bleeding	Modify restrictions to include the Department of OB/GYN for inpatients with heavy intrauterine bleeding.
Tocilizumab (Actemra®) Subcutaneous Injection	Monoclonal Antibody	Systemic Sclerosis-Associated Interstitial Lung Disease	Modify restrictions to include the Department of Rheumatology and Immunologic Disease and Pulmonary for the treatment of systemic sclerosis-associated interstitial lung disease in the outpatient setting. There are no restrictions for continuation for inpatients for this indication.

SICU=Surgical intensive care unit PGY=Post-graduate year ICU=Intensive care unit PTCL=Peripheral T-cell lymphoma
OB/GYN=Obstetrics/Gynecology

Product Standardizations to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Details**
Long-Acting Muscarinic Antagonist/ Long-Acting Beta Agonist (LAMA/LABA) Inhaler Therapeutic Interchange	LAMA/LABA	COPD	The LAMA/LABA Inhaler Therapeutic Interchange has been modified to substitute tiotropium bromide/ olodaterol (Stiolto® Respimat®) for umeclidinium/vilanterol (Anoro® Ellipta®) due to an easier mode of drug delivery. Details are in Lexicomp.

LAMA=Long-acting muscarinic agent LABA= Long-acting beta-adrenergic agent COPD=Chronic obstructive pulmonary disease

Removals from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Details**
Chloramphenicol Intravenous Injection	Antibiotic	Various Infections	The sole manufacturer discontinued chloramphenicol production.
Desflurane Inhalation	Inhaled Anesthetic	Anesthesia Induction and Maintenance	Desflurane has a much higher global warming potential than alternative agents such as isoflurane, nitrous oxide, and sevoflurane. Due to the climate impact, low usage, and availability of alternative agents, a decision was made to remove desflurane from the CCHS Adult Formulary.

Process Changes to the Adult CCHS Formulary			
Process	**Pharmacologic Class**	**Formulary Use**	**Details**
Hepatitis C Pharmacist Consult Agreement Updates	Anti-Viral Agents	Hepatitis C Infection	Updates to this Consult Agreement were approved.
Infectious Disease Standard Operating Procedure for Pharmacist Consult Agreements	Anti-Infective Agents	Various Infections	Outpatient ambulatory infectious disease consult agreements (travel medicine, sexually transmitted infection prophylaxis and treatment, community-based antimicrobial therapy services and injectable antiretroviral therapy) were consolidated to have all services in one agreement entitled "Infectious Diseases Standard Operation Procedure for Pharmacist Consult Agreements." Individual consult agreements will be retired.
Tocilizumab (Actemra®) Intravenous Injection Dose Rounding	Interleukin-6 Receptor Antagonist	Various Indications	Dose rounding was approved. Rounded doses will not exceed a 10% change from the ordered dose. Details are in Lexicomp.
Vancomycin Oral Capsules	Antibiotic	Clostridium difficile Infection	A switch from compounded oral vancomycin solution to the commercially available oral vancomycin capsules was approved based on reduced pharmacy operation compounding time, reduction in plastic waste from unit dose cup and syringes dispensing, and cost reduction for the capsules. Vancomycin capsules cannot be opened for feeding tube administration. Patients who are unable to swallow and those who have feeding tubes may still receive the compounded oral vancomycin solution.

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Angiotensin II (Giapreza®) Intravenous Injection	Vasoactive Agent	Septic or Vasodilatory Shock	Restricted to Staff Physicians from the Department of Pediatric Critical Care (PICU/PCICU) for patients with septic or other vasodilatory shock receiving at least two vasopressors
Hydroxocobalamin (Cyanokit®) Intravenous Injection	Antidote	Cyanide Toxicity	Restricted to the treatment of suspected or known cyanide toxicity
Smallpox and Monkeypox Vaccine (Jynneos®) Injection	Live Vaccine	Prevention of Smallpox and Monkeypox	No Restrictions
Upadacitinib (Rinvoq®) Oral Tablets	Janus Kinase Inhibitor	Inflammatory Bowel Disease	Restricted to Staff Physicians from the Department of Pediatric Gastroenterology for use in patients meeting all of the following criteria: 1) Patient must have failed at least one or have a contraindication to Tumor Necrosis Factor blocking agents. 2) Patient must be at least 12 years of age. 3) Insurance coverage must be verified prior to inpatient dispensing. 4) Continuation of therapy from home is not restricted.

PICU=Pediatric intensive care unit PCICU=Pediatric cardiac intensive care unit

Removals from the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Details**
Chloramphenicol Intravenous Injection	Antibiotic	Various Infections	See "Removals from the Adult CCHS Formulary" for details,
Desflurane Inhalation	Inhaled Anesthetic	Anesthesia Induction and Maintenance	See "Removals from the Adult CCHS Formulary" for details.
Sodium Nitrite and Sodium Thiosulfate (Nithiodote™)	Antidote	Cyanide Toxicity	Due to sodium nitrite and sodium thiosulfate's adverse effect profile and the addition of hydroxocobalamin (Cyanokit®) to the Pediatric Formulary, a decision was made to remove Nithiodote™.

Changes to Restrictions of the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes**
Alteplase (Activase®) Intrapleural Instillation	Thrombolytic Agent	Loculated Pleural Effusions/ Empyema	Modified restrictions to include the administration by physicians or another licensed independent practitioner from Pediatric Critical Care, Pediatric Surgery, or Interventional Radiology when used for treating loculated pleural effusions/empyema. It may be administered on any floor.
Dornase Alfa (Pulmozyme®) Inhalation	Mucolytic Agent	Pulmonary Atelectasis	Modified restrictions to include the Department of Pediatric Pulmonology and the Department of Pediatric Critical Care (PICU/PCICU) for management of atelectasis in patients not responsive to other conventional therapies (e.g., saline, N-acetylcysteine) 1) Use is limited to a 7-day course. 2) Continuation of home therapy is not restricted.
Ibuprofen Oral Tablets and Liquid	NSAID	PDA closure Pain Control	The following restrictions will be implemented to guide prescribing and Epic alerting: 1) There are no age restrictions when ibuprofen is being used to treat PDA closure 2) Ibuprofen may be administered to patients 2 months of age and older as part of the PCICU Post-Op Protocol 3) For all additional indications not included above, ibuprofen use is restricted to patients at least 3 months of age AND weighing at least 5 kg a) One-time doses are not restricted.
Micafungin Intravenous Solution	Echinocandin Antifungal	Fungal Infections	Modified restrictions to include the Department of Pediatric Hematology/ Oncology and Bone Marrow Transplant for **prophylaxis** indications Note: Use for **treatment** will still be restricted to the Department of Pediatric Infectious Diseases.
OnabotulinumtoxinA (Botox®) Injection	Neuromuscular Blocking Agent	Anorectal and Abdominal Wall Malformations	Modified restrictions to include the Department of Pediatric Surgery for anorectal malformations or abdominal wall malformations

PICU=Pediatric intensive care unit PCICU=Pediatric coronary intensive care unit NSAID=Nonsteroidal anti-inflammatory agent
PDA=Patent ductus arteriosus

Process Changes to the Pediatric CCHS Formulary			
Process	**Pharmacologic Class**	**Formulary Use**	**Details**
Pharmacy Pediatric Vancomycin Dosing Service and Monitoring Guideline Updates	Antibiotic	Various Infections	Updates to this Dosing Service were approved.
Vancomycin Oral Capsules	Antibiotic	Various Infections	See "Process Changes to the Adult CCHS Formulary" for details.

Product Standardizations to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Details**
Phenylephrine Nasal Spray Therapeutic Interchange Update	Decongestant	Allergy Colds	The updated version includes an option for scheduled therapy of phenylephrine nasal spray in neonates. Details are in Lexi-comp.