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Two New Weight Loss Therapies

By: **Brian S. Hoffmaster, Pharm.D.**

Introduction: The World Health Organization (WHO) classifies obesity as a chronic disease associated with significant healthcare issues.¹ In the United States, approximately 64.5% of adults are overweight, 30.5% are obese, and 4.7% are severely obese. The consequences of obesity include significant sleep, cardiovascular, pulmonary, digestive, endocrine, obstetric, and orthopedic disorders.^{2,3} Effective treatment of obesity will likely demonstrate favorable improvement in cardiovascular and metabolic risk factors, as well as reduced medical care costs as a result of weight loss.³ The Food and Drug Administration (FDA) recognizes obesity as a chronic disease state and expects new therapies to demonstrate long-term safety and efficacy in large, diverse populations.^{3,4} In the past 13 years, the approval of various weight loss treatments has been stalled due to lack of long-term safety and concerns related to the market with-

drawal of various antiobesity agents (e.g., fenfluramine, dexfenfluramine, sibutramine) which caused serious cardiovascular effects.³⁻⁵ However, the healthcare risks associated with obesity are now considered extremely serious and have prompted the FDA's recent approval of two new agents for weight loss: lorcaserin (Belviq®; Arena Pharmaceuticals) and phentermine/topiramate (Qsymia™; Vivus Pharmaceuticals).⁶ This review will answer some commonly asked questions about these agents.

How do lorcaserin and phentermine/topiramate work?

- These agents are the only central nervous system (CNS) acting pharmacotherapies for obesity indicated for long-term use.³ Older prescription weight loss therapies are indicated for short-term use secondary to concerns of transient efficacy and

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Intravenous Acetaminophen – Is it Worth the Cost?

By: **Mahmoud Ammar, Pharm.D.**

Introduction: One of the most widely used over-the-counter pain relievers and fever reducers is acetaminophen. Acetaminophen, also known as paracetamol, is commercially available in many formulations (e.g., tablet, capsule, liquid suspension, suppository, and parenteral injection).¹ This article discusses the major differences between intravenous (IV) acetaminophen and other acetaminophen dosage forms. Additionally, the efficacy and safety of IV acetaminophen and its economic impact will be reviewed.

In November 2010, the Food and Drug Administration (FDA) approved IV acetaminophen (Ofirmev®; Cadence Pharmaceuticals, Inc.) in both adults and children at least 2 years of age for the management of mild-to-moderate pain and the management of moderate-to-severe pain when used in combination with opioid analgesics. Intravenous acetaminophen is also FDA-approved for fever reduction.²

Pharmacodynamics: Although acetaminophen is known to be an effective analgesic, its antipyretic and

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physical dependency potential.

- Lorcaserin is a first-in-class serotonin 2C receptor agonist targeted to increase satiety.⁷ Its mechanism of action is not fully understood, but selective activation of the serotonin 2C receptor on anorexigenic neurons in the hypothalamus is thought to cause patients to feel full sooner and eat less.
- Phentermine/topiramate is a new, extended-release combination of two drugs that already have separate FDA approval for other indications.⁸ Phentermine exhibits sympathomimetic appetite suppressive effects, similar to older weight loss therapies.⁹ Topiramate is the first weight loss therapy to target appetite suppression and increase satiety as a gamma-aminobutyric acid (GABA) agonist and glutamate and carbonic anhydrase antagonist.

How are they dosed and how long does it take for these drugs to work?

- Lorcaserin is taken as one 10-mg tablet, twice daily.⁷ It should be discontinued if a 5% weight loss from baseline is not observed at 12 weeks of therapy. There are no specific recommendations regarding how to discontinue therapy.

- All strengths of phentermine/topiramate, which are extended-release capsules, are always taken once daily in the morning to avoid insomnia.⁹ Patients start at a dose of 3.75 mg/23 mg daily for 2 weeks before titrating to 7.5 mg/46 mg daily for 12 weeks. If patients have a weight loss of 3% from baseline after 12 weeks of this dosage, it should be continued. Otherwise, therapy should be discontinued or the dose should be titrated with 2 weeks of 11.25 mg/69 mg daily followed by 15 mg/92 mg daily for 12 weeks. It should be discontinued if a 5% weight loss from baseline is not observed at 12 weeks of this dosage. Discontinuation should not be abrupt due to risk of seizures. Dosing information is outlined in Figure 1.

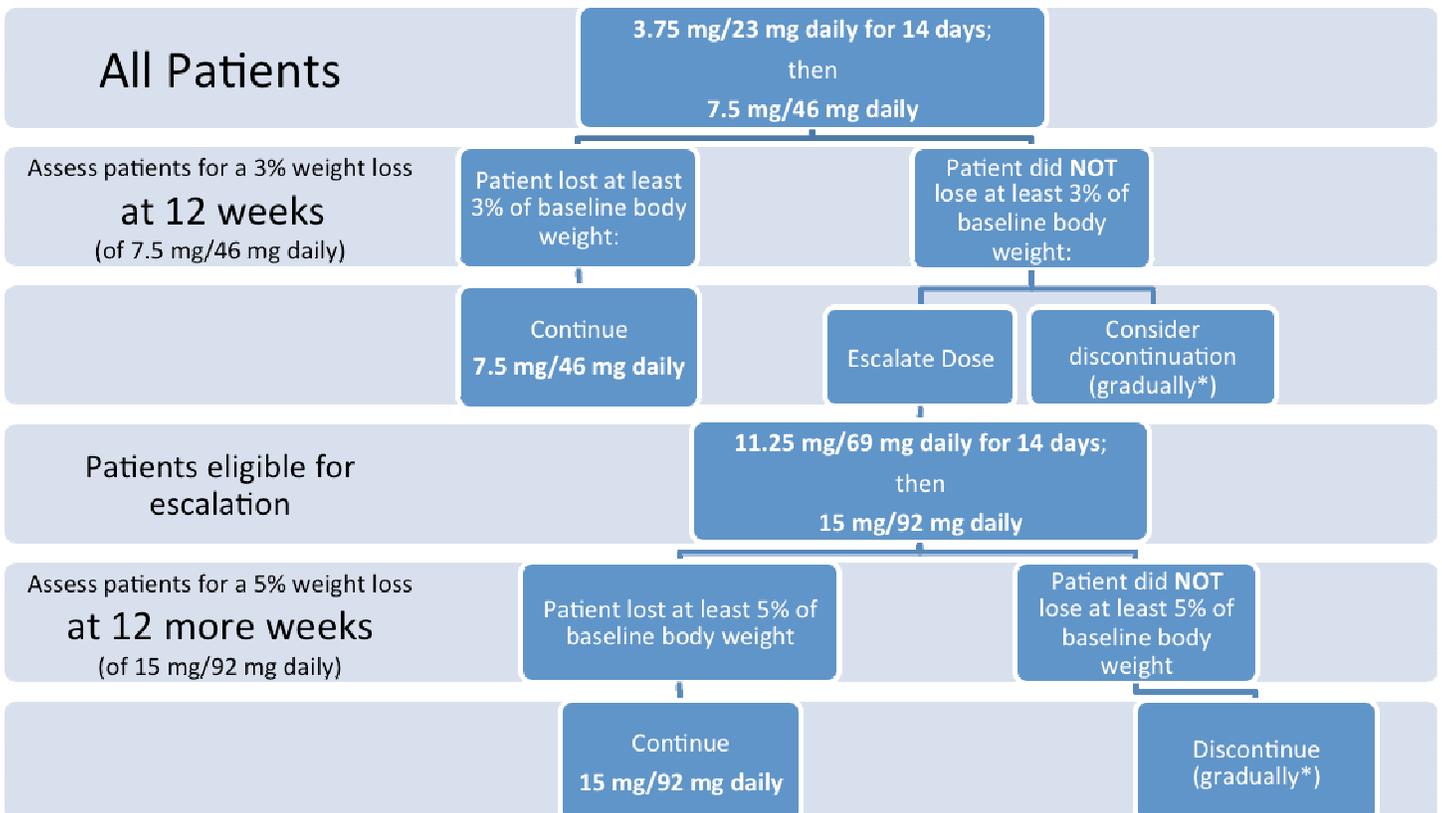
How long are these agents to be taken?

- Both lorcaserin and phentermine/topiramate are indicated for chronic weight management. The agents should not be discontinued unless they are ineffective, as described above, or adverse effects warrant cessation.^{7,9}

What is the expected effect?

- In clinical trials, lorcaserin and phentermine/topiramate demonstrated an increased portion of

Figure 1: Phentermine/Topiramate Dosing Decision Tree^{9,20}



* When discontinuing phentermine/topiramate, patients should take one capsule every other day for 1 week before complete discontinuation, regardless of dosage strength, to avoid seizure precipitation.

patients reaching 5% weight reduction compared with placebo.¹⁰⁻¹⁴

- Lorcaserin produced an average weight loss of seven pounds more than placebo over 1 year of therapy.⁷ In non-diabetics, significantly more lorcaserin patients achieved at least 5% weight reduction compared to those taking placebo (47.1% versus 22.6%, respectively; P<0.001). In a separate study of diabetic patients, significantly more lorcaserin patients achieved at least 5% weight reduction (37.5% versus 16.1%, respectively; P<0.001).¹²
- Phentermine/topiramate combination produced an average weight loss ranging from 7 to 21 pounds more than placebo when given in various dosages over

1 year of therapy.⁹ Significantly more patients achieved at least 5% weight reduction when given phentermine/topiramate at 15 mg/92 mg than placebo (66.7% versus 17.3%, respectively; P<0.0001).¹³ Significantly more patients with comorbidities (e.g., diabetes) achieved at least 5% weight reduction when given phentermine/topiramate at 7.5 mg/46 mg or 15 mg/92 mg than placebo (62% or 70% versus 21%, respectively; P<0.0001).¹⁴

Who can take these agents?

- Both lorcaserin and phentermine/topiramate are indicated as adjunct to a reduced-calorie diet and increased physical activity for chronic weight

Table 1: Key Differences Between Weight Loss Agents^{7,9,21}

	Lorcaserin (Belviq®)	Phentermine/Topiramate (Qsymia™)
FDA-approved Indication	Adjunct to reduced-calorie diets and increased physical activity for chronic weight management in the following adult patients: <ul style="list-style-type: none"> • Obese (BMI ≥ 30 kg/m²) or • Overweight (BMI ≥ 27 kg/m²) with at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes) 	
Bioavailability	Readily absorbed; specific bioavailability unknown	
Metabolism	Extensively hepatic to inactive metabolites	Non-extensive hepatic metabolism
Maintenance Dose	10 mg twice daily	7.5 mg/46 mg or 15 mg/92 mg once daily
Dosage Forms	10 mg tablet	Extended-release capsules: 3.75 mg/23 mg capsules (for titration only)* 7.5 mg/46 mg capsules 11.25 mg/69 mg capsules (for titration only)* 15 mg/92 mg capsules
Dose in Renal Impairment	Use with caution; do not use in patients with severe impairment or end stage renal disease (Use Ideal Body Weight in CrCl calculation)	Dosing should not exceed 7.5 mg/46 mg once daily in patients with CrCl< 50 mL/min (Use Actual Body Weight in CrCl calculation)
Dose in Hepatic Impairment	Use with caution in severe hepatic impairment (Child-Pugh score > 9)	Dosing should not exceed 7.5 mg/46 mg once daily in moderate hepatic impairment (Child-Pugh score 7-9)
Select Drug Interactions	Serotonergic drugs due to risk of serotonin syndrome	Oral contraceptives (to cause spotting, but not an increased risk of pregnancy), CNS depressants (potentiating CNS depressant effects), non-potassium sparing diuretics (potentiating hypokalemia)
Cost	Cost data are unavailable at this time	For thirty 3.75 mg/23 mg capsules: \$144.00 For thirty 7.5 mg/46 mg capsules: \$162.74 For thirty 11.25 mg/69 mg capsules: \$195.28 For thirty 15 mg/92 mg capsules: \$220.68

*3.75 mg/23 mg capsules are used for 2 weeks at therapy initiation and should be prescribed in conjunction with initial prescription for 7.5 mg/46 mg capsules; 11.25 mg/69 mg capsules are only used for 2 weeks as transition from 7.5 mg/46 mg to 15 mg/92 mg capsules. BMI=body mass index CNS=central nervous system CrCl=creatinine clearance FDA=Food and Drug Administration

management in the following adult patients:^{7,9,15,16}

- Obese (body mass index [BMI] ≥ 30 kg/m²)
- Overweight (BMI ≥ 27 kg/m²) with at least one weight-related comorbid condition, (e.g., hypertension, dyslipidemia, type 2 diabetes)

Who should not take these agents?

- All weight-loss therapies are contraindicated in pregnant women because weight loss offers no potential benefit and may result in fetal harm.^{7,9} Both lorcaserin and phentermine/topiramate are rated as pregnancy category X since they have demonstrated fetal abnormalities in animals or humans.^{7,9,16,17}
- Combination phentermine/topiramate should not be used in patients with glaucoma, hyperthyroidism, hypersensitivity to sympathomimetic amines, or those taking monoamine-oxidase inhibitors (MAOIs).⁹

What are the common side effects of these agents?

- Adverse effects of lorcaserin (incidence $\geq 5\%$) may include: headache, dizziness, fatigue, nausea, dry mouth, and constipation; hypoglycemia, headache, back pain, cough, and fatigue may be experienced in diabetics.
- Adverse effects of phentermine/topiramate (incidence $\geq 5\%$) may include: paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth.⁹

Are there post-marketing requirements?

- Arena Pharmaceuticals, Inc. is required to complete studies of lorcaserin to determine:¹⁵
 - Potential for major adverse cardiovascular events in obese and overweight subjects with cardiovascular disease or multiple cardiovascular risk factors
 - Effects on learning, memory, motor development, physical development, sexual maturation, mating, and fertility in juvenile animals
- Vivus Pharmaceuticals, Inc. is required to complete studies of phentermine/topiramate to determine:¹⁶
 - Potential for major adverse cardiovascular events in obese and overweight subjects with cardiovascular disease or multiple cardiovascular risk factors
 - Effects on the general nervous system, behavior, learning and memory, ocular toxicity, and bone/teeth development in juvenile animals
 - Frequency of pregnancy in women taking phentermine/topiramate, the risks and rates of congenital malformations, and a comparison of the risks and rates between women who were and were not exposed to phentermine/topiramate in pregnancy
 - Effect on changes in renal function

Are these agents available and will there be any barriers to obtaining them?

- Lorcaserin is not yet available because it can produce feelings of euphoria, hallucinations, dissociations, and cognitive impairment, and is waiting for controlled substance scheduling by the Drug Enforcement Agency (DEA).^{7,15} Lorcaserin will be available without a Risk Evaluation and Mitigation Strategy (REMS) program.
- Phentermine/topiramate is now available by mail order through certified pharmacies.¹⁹ Since topiramate is a known teratogen, it has been approved with a REMS program to prevent its use in pregnancy.^{9,16} Monthly pregnancy tests will be required in female patients. Patients and pharmacists are directed to the manufacturer's website (<http://www.qsymia.com/>) with questions about obtaining the product. It has been scheduled by the DEA as a schedule IV controlled substance because phentermine exhibits abuse and dependence potential.⁹

Summary: A summary of key differences between the agents is available in Table 1. Phentermine/topiramate is the only agent available to target weight loss with two separate mechanisms of action. In clinical trials, phentermine/topiramate produced weight loss in more patients and to a greater extent than lorcaserin over a 1 year period. However, phentermine/topiramate is only available through specialty pharmacies, because of various REMS requirements, and its dosing schedule is relatively complicated.^{5,9} Lorcaserin use, although not yet associated with valvular adverse effects, warrants precaution for this potentially serious adverse effect.^{7,10-12,18} Additionally, lorcaserin therapy, which must be given twice daily, may be challenging for patients from an adherence standpoint compared to once daily phentermine/topiramate.^{7,9} These drugs, which should always be used with life-style modification, serve as helpful adjuncts for moderate weight loss. Significant health and healthcare cost benefits are eagerly anticipated with these new antiobesity therapies.

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Intravenous Acetaminophen (Continued from page 1)

analgesic mechanism of action is not fully understood.³ Researchers believe that acetaminophen works both centrally and peripherally in the body. Centrally, acetaminophen exerts its antipyretic effects by directly acting on the hypothalamic heat-regulating centers that result in an increased dissipation of body heat. Acetaminophen also inhibits the production of prostaglandins in the central nervous system, which results in an anti-inflammatory effect. Peripherally, it is believed that acetaminophen blocks impulse generation and inhibits prostaglandin production.⁴

Pharmacokinetics: The pharmacokinetics of IV acetaminophen have been evaluated in clinical trials. Subjects in these trials ranged from premature neonates to adults ≤60 years of age.² When administered intravenously, acetaminophen has an onset of action of 5-10 minutes for pain relief and 30 minutes for fever reduction. The peak analgesic effect of IV acetaminophen is documented as 1 hour and the duration of action is 4-6 hours and >6 hours for its analgesic and antipyretic effects, respectively. In contrast to IV acetaminophen, oral and rectal acetaminophen administration have different pharmacokinetics profiles. The onset of action for both the oral and rectal acetaminophen is less than 1 hour, and the time to the peak effect of oral acetaminophen is 1 hour while the time to the peak effect for the rectal acetaminophen is 1-3 hours. The duration of action of both the oral and rectal administration is the same (4-6 hours).³

Pharmacokinetic studies comparing IV acetaminophen to oral acetaminophen showed that IV acetaminophen achieved a 70% higher maximum plasma concentration at the end of the infusion time compared to oral acetaminophen. Nevertheless, the overall exposure (area-under-the-concentration-time-curve or AUC), between both routes of administration were similar.² On the other hand, pharmacokinetic trials comparing IV acetaminophen to rectal acetaminophen concluded that the IV route achieved a higher maximum plasma concentration and overall exposure compared to the rectal dosage form.⁵ Intravenous acetaminophen is associated with less variability in absorption than oral acetaminophen formulations; consequently, IV acetaminophen produces a more predictable plasma concentration.⁶ Despite the fact that IV acetaminophen has a more predictable pharmacokinetic profile, a single dose of rectal acetaminophen has a longer analgesic effect when compared to the IV dosage form possibly due to a longer period of the effect-site concentration maintained for the rectal than the IV route.⁷

Clinical Trials: Intravenous acetaminophen has been studied for efficacy in both adults and children for the management pain and fever. Intravenous acetaminophen has been available overseas since 2001 under the trade name Perfolgan® (Bristol-Myers Squibb, Inc) and most of the IV acetaminophen trials were conducted outside the United States.⁸ Two meta-analyses evaluated trials that compared all forms of acetaminophen in combination with patient controlled analgesia (PCA) after major surgery.^{9,10} Remy and colleagues included seven randomized, placebo-controlled trials; six of these studies reported IV acetaminophen administration.⁹ While Elia and coworkers included 52 trials, ten of these trials reported administration of oral and IV acetaminophen.¹⁰ These two analyses reported that acetaminophen administered via different routes, including the IV route, after surgery significantly reduced morphine requirement by almost 20%. However, this reduction was not accompanied by a significant reduction in opioid-related side effects such as postoperative nausea and vomiting (PONV), urinary retention, sedation, and respiratory depression.^{9,10}

Romsing and colleagues conducted a meta-analysis that included 24 studies comparing the analgesic effects of the three different dosage forms of acetaminophen.¹¹ The analysis concluded that both rectal and IV acetaminophen were effective in managing postoperative pain. There were not enough data to compare the results of the different dosage forms. In addition, the review showed that the coadministration of nonsteroidal anti-inflammatory medications (NSAIDs) with acetaminophen improved pain relief. However, the addition of acetaminophen to a pain-relieving NSAIDs regimen had a less predictable effect.

Pettersson and colleagues evaluated whether IV acetaminophen (1000 mg every 6 hours) compared to oral acetaminophen (1000 mg every 6 hours) reduced the consumption of opioids and their side effects without an increase in pain during the stay of 77 subjects in an Intensive Care Unit (ICU).¹² The authors concluded that IV acetaminophen had a limited opioid-sparing effect but without a significant reduction in opioid side effects. There was no significant difference in the visual analog pain score (VAS) between both groups. Additionally, 65% of all patients had a VAS score above 3 during the first 2 hours post acetaminophen administration which may lead clinicians to question the efficacy of this pain therapy.

Similar efficacy results were also reported by Uvarov and coworkers who compared the efficacy of IV and rectal acetaminophen in 75 patients who were under-

going elective or emergent thoracotomy.¹³ All patients received epidural auto-analgesia and intramuscular injections of ketorolac. The authors concluded that the resting VAS did not differ between all groups.

Safety: Intravenous, oral, and rectal acetaminophen have similar safety profiles. In general, IV acetaminophen was well tolerated in clinical trials. The most common adverse events reported $\geq 5\%$ in adult patients were nausea, vomiting, headache, and insomnia. While the most common side effects reported $\geq 5\%$ in pediatric patients were nausea, vomiting, constipation, pruritis, agitation, and atelectasis.² European reports showed there is a greater chance of dosing errors when administering IV acetaminophen when compared to other routes especially in the pediatric population.¹⁴ This was the result of calculating the dosage in milligrams and administering the IV solution in milliliters instead.

Dosage: The dose of IV, oral, and rectal acetaminophen for the management of pain or fever is summarized in Table 1. Each IV acetaminophen dose should be given as a 15-minute infusion.² One of the concerns with this infusion time is that it might affect the length of patient stay in the post-anesthesia care units (PACU).¹⁵ The fluid intake associated with administration of IV acetaminophen might also be a challenge for fluid restricted patients.

How Supplied: Intravenous acetaminophen is supplied in a 100-ml glass vial which contains 1000 mg of acetaminophen.²

Stability: According to product labeling, the IV acetaminophen vials should be used within 6 hours of opening.² An extended stability study found that IV acetaminophen was physically and chemically stable for up to 84 hours in opened vials.¹⁶ However according to the USP 797 guidelines, maximum exposure time for low-risk level compounded sterile products stored at room temperature is 48 hours. Therefore, stability for IV acetaminophen products was extended from 6 hours to 40 hours; this change is noted in Epic.

Cost: The cost of a 1000 mg every 6 hours IV acetaminophen regimen is several times higher than the cost of regimens utilizing the oral or rectal formulation. On average, the cost is $> \$10.00$ per IV dose compared to $< \$1.00$ per oral dose.

Restrictions: At Cleveland Clinic, IV acetaminophen has the following formulary restrictions: IV acetaminophen must be prescribed by a Staff Physician and it

must not be used as a first-line therapy. Furthermore, it must have a specific indication for use such as patient is NPO or cannot receive NSAIDs due to risk of bleeding. It can only be ordered for 24 hrs, but can be repeated (reordered) daily. Additionally, other than the PACU dispensing cabinets (e.g., Pyxis machine), no other Pyxis machine will stock this item. These restrictions are in place to ensure appropriate use of IV acetaminophen. Please refer to the on-line formulary for a list of pediatric restrictions on IV acetaminophen.

Conclusion: Intravenous acetaminophen has documented safety and efficacy as an analgesic agent in patients aged 2 years and older. Intravenous acetaminophen has been publicized as an opioid-sparing analgesic with a potential of reducing opioid-related side effects. In general, IV acetaminophen reduces opioid administration by around 20% but it is not associated with a constant sparing of opioid-related side effects. Even though IV acetaminophen has a faster onset of action, the overall exposure of IV acetaminophen is similar to the overall exposure of acetaminophen when administered via the oral route. Furthermore, IV acetaminophen is prone to dosing errors, especially in the pediatric population.

Unfortunately, there has not been a full evaluation of the economic impact of IV acetaminophen in the United States. However, in an era of cost-effectiveness, IV acetaminophen does not appear to have any clinical benefit over oral and rectal acetaminophen except in patients who require IV administration. Given the high drug cost and inconsistent benefit, IV acetaminophen should be reserved for patients who cannot take acetaminophen via oral or rectal routes and patients who cannot tolerate the other IV non-opioid analgesics.

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Table 1 : Dosing of Acetaminophen for Pain and Fever^{2,3}

Formulation	Age	Dose	Maximum Dose
IV*	Adults < 50 kg Children 2-12 years old†	15 mg/kg every 6 hours 12.5 mg/kg every 4 hours	75 mg/kg/day (≤ 3.75 grams/day)
	Adult >50 kg	650 mg every 4 hours 1000 mg every 6 hours	4 grams/day (maximum single dose 1000 mg)
Oral / Rectal	Adults	325-650 mg every 4-6 hours 1000 mg 3-4 times per day	4 grams/day
	Infants/Children <12 years	10-15 mg/kg/dose every 4-6 hours as needed (oral) 10-20 mg/kg/dose every 4-6 hours as needed (rectal)	Do not exceed 5 doses 2.6 g/day (oral and rectal)

*Given over 15 minutes

†IV acetaminophen is only approved for children aged 2 years or older

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FORMULARY UPDATE

Restriction Changes to Adult CCHS Formulary			
Drug	Pharmacologic Class	Formulary Use	Change in Restriction
Certolizumab pegol (Cimzia®)	TNF Inhibitor	Crohn's disease Rheumatoid arthritis	Original restriction: The Department of Gastroenterology for out-patient use in adult patients only The Pediatric Department of Gastroenterology for use in pediatric patients The powder version was added for outpatient use only for patients who need administration by a healthcare professional
Prothrombin complex concentrates (Profilnine®)	Blood Product Derivative	Warfarin-related life-threatening hemorrhage (e.g., ICH) per protocol	Original restriction: Department of Neurology and Neurosurgery for warfarin-related life-threatening intracranial hemorrhage Restrictions are expanded to include Emergency Room Physicians and Intensivists for warfarin-related life-threatening hemorrhage (e.g., ICH) per protocol
Rabbit antithymocyte globulin (Thymoglobulin®)	Immunosuppressant Agent	Immunosuppression	Original restriction: Transplant Services Use Only Restrictions expanded to include Hematology/Oncology for aplastic anemia
Rivaroxaban (Xarelto®)	Oral anticoagulant Factor Xa Inhibitor	DVT/PE treatment/prophylaxis	Remove all restrictions based on indication

DVT=Deep vein thrombosis ICH=Intracranial hemorrhage PE=Pulmonary embolism TNF=Tumor Necrosis Factor

Additions to Adult CCHS Formulary			
Drug	Pharmacologic Class	Formulary Use	Restriction/Comments
Ado-trastuzumab ematansine (Kadcyla™)	Antineoplastic antiHER2	Treatment of HER2-positive metastatic breast cancer	Restricted to Hematology/Oncology for outpatient use only
Apixaban (Eliquis®)	Oral direct, selective and reversible Xa inhibitor	To reduce the risk of stroke and DVT in patients with nonvalvular atrial fibrillation	No restrictions
Buprenorphine and naloxone (Suboxone®) Sublingual Film Tablets	Opioid partial agonist	Pain control maintenance treatment for opioid dependence	Brandname Suboxone® sublingual tablets were discontinued, the film tablets were added as an alternative to prevent delays in therapy until generic version of Suboxone® is available
Hydroxocobalamin (Cyanokit®)	Antidote	Cyanide poisoning	Standardize cyanide antidote kits throughout CCHS
Prothrombin complex concentrates (FEIBA®)	Blood product derivative	Hemophilia treatment Reversal of oral anticoagulants	Restricted to Hematology Specific details to reverse select anticoagulants (e.g., dabigatran, rivaroxaban, and apixaban) will be in CCAMP
Viokace®	Pancreatic enzyme supplement	Pancreatic enzyme supplementation Unclog feeding tubes	FDA-approved product will be added across CCHS

CCAMP= Cleveland Clinic Anticoagulation Management Protocol FDA= Food and Drug Administration

Additions to Pediatric CCHS Formulary			
Drug	Pharmacologic Class	Formulary Use	Restriction/Comments
Active Leptospermum Honey/Medical Grade Honey (MediHoney™)	Wound Dressing	Wound care management	Restricted as a second-line agent after failure of conventional therapy in patients at least 35 weeks post-conceptual age and at least 14 days of age
Deferasirox (Exjade®)	Chelating Agent	Management of iron overload	Restricted to the Departments of Pediatric Hematology/Oncology and Bone Marrow Transplant
Sodium Nitrate/Sodium Thiosulfate (Nithiodote®)	Antidote	Cyanide Poisoning	Standardization of cyanide poisoning kits throughout CCHS. This kit is FDA-approved in the pediatric population

FDA=Food and Drug Administration