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From the Department of Pharmacy

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Andexanet Alfa: A New Factor Xa Inhibitor Reversal Agent

By: Emily Limberg, Pharm.D.

Introduction: Warfarin (Coumadin®; Bristol-Myers Squibb) was the only oral anticoagulant available for decades, and despite the advent of the novel oral anticoagulants (NOACs), it has remained popular partly because there were not specific reversal agents for the NOACs.[1] The Food and Drug Administration (FDA) approved idarucizumab (Praxbind®; Boehringer Ingelheim) for reversal of the direct thrombin inhibitor dabigatran (Pradaxa®; Boehringer Ingelheim) in October 2015, leaving the factor Xa inhibitors as the primary group of anticoagulants without a specific reversal agent. However there are new data demonstrating the reversal of these factor Xa inhibitors by an investigational agent, andexanet alfa (AndexXa®; Portola Pharmaceuticals).

Mechanism of Action: Andexanet alfa is a modified human recombinant factor Xa decoy protein that reverses anticoagulation from direct factor Xa inhibitors such as apixaban (Eliquis®; Bristol-Myers Squibb), edoxaban (Savaysa®; Daiichi Sankyo), and rivaroxaban (Xarelto®; Janssen).[1-3] Andexanet alfa lacks the pro-coagulant activity of endogenous factor Xa due to the substitution of an alanine for serine in the active site; however, it still has a high affinity for factor Xa inhibitors and binds to them in a 1:1 ratio. Endogenous factor Xa activity is restored when andexanet alfa binds to the factor Xa inhibitors, restoring thrombin generation, and allowing coagulation to resume. In addition, andexanet alfa lacks the domain that allows binding to the cell membrane, preventing this drug from forming complexes with tissue factor and factor VIIa and thus from activating the coagulation cascade.[1,2] Finally, andexanet alfa has activity against fondaparinux (Arixtra®; GlaxoSmithKline) and low molecular weight heparins (LMWHs), which indi-

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Lixisenatide in Uncontrolled Type 2 Diabetes Mellitus

By: Rebekah Krupski, Pharm.D.

Background: Lixisenatide(Adlyxin™; Sanofi-Aventis) is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that received Food and Drug Administration (FDA) approval on July 27, 2016.[1] Similar to the existing GLP-1 RAs on the market, it is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).[2] The GLP-1 RA class of agents is recommended as an option for add-on therapy if the HbA_{1c} target is not achieved after 3 months of monotherapy with metformin.[3]

Mechanism of Action: Lixisenatide is another short-acting analog of human GLP-1 with a half-life of approximately 3 hours, compared to exenatide (Byetta®; Amylin Pharmaceuticals) with a half-life of 2.4 hours.[2,4] Mechanistically, it increases glucose-dependent insulin release, decreases glucagon secretion, slows gastric emptying, and increases satiety. Of note, lixisenatide lowers HbA_{1c} with a once-daily administration, compared to twice daily dosing with exenatide.[2,4]

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rectly inhibit factor Xa, because it can also bind the antithrombin that forms a complex with both of those agents. However, andexanet alfa may not completely reverse enoxaparin (Lovenox®; Sanofi-Aventis), which still has activity against factor IIa and therefore may require protamine for full reversal.[2]

Pharmacokinetics: Andexanet alfa has an onset of action of 2 minutes. Its terminal half-life is 6 hours, but it has a pharmacodynamic half-life of only 1 hour.[1,3]

Clinical Efficacy: Two randomized, double-blind, placebo-controlled Phase 1 trials (ANNEXA-A and ANNEXA-R) were conducted in order to evaluate the efficacy and safety of andexanet alfa in healthy volunteers between the ages of 50 and 75 years.[4] Each study was designed in two parts, in the first part participants were randomized to receive an andexanet alfa bolus only or placebo and in the second part, participants were randomized to receive a bolus dose followed by a continuous 2 hour infusion or placebo. Prior to randomization, subjects were given Factor Xa inhibitor therapy for a few days, subjects in the ANNEXA-A trial received apixaban 5 mg twice day, while those in the ANNEXA-R trial received rivaroxaban 20 mg daily. The primary endpoint for each study was the mean percent change in anti-factor Xa activity. In both studies, andexanet alfa significantly reduced anti-factor Xa activity; this effect occurred within 2 to 5 minutes and lasted 2 hours after the bolus and 1 to 2 hours after the end of the infusion depending on the anticoagulant administered. A Phase 3 study is currently underway to evaluate the safety and efficacy of andexanet alfa in patients prescribed factor Xa inhibitors that present with acute major bleeding.

Safety: No serious adverse events or thrombotic events were reported during the aforementioned studies.[4] The most common adverse events were constipation, dysgeusia, and flushing. Urticaria occurred in one patient in each study. One major concern was the possibility for antibody development to andexanet alfa, factor X, or factor Xa.[2] However, antibodies to either factor X or factor Xa did not develop, but non-neutralizing antibodies to andexanet alfa were found in 17% of patients. Although no thrombotic events have been reported, there is a concern that andexanet alfa may have a pro-coagulant effect as its use has been linked to temporary elevations of D-dimer, tissue factor pathway inhibitor, and prothrombin fragments 1 and 2.[2,4]

Dosing and Administration: In the clinical trials, a 400 mg bolus of andexanet alfa given at a rate of 30 mg/minute followed by a continuous 2 hour infusion administered at 4 mg/minute was utilized to reverse apxiaban.[4] Because rivaroxaban has a larger volume of distribution and higher plasma concentration level, the reversal dose of andexanet alfa was increased to 800 mg for the bolus given at a rate of 30 mg/minute, followed by an infusion of 8 mg/minute over 2 hours.[1,4,5] Appropriate dosages for the reversal of edoxaban, fondaparinux, and enoxaparin have not yet been established.[2]

FDA Approval Status: Portola Pharmaceuticals Inc. initially sought accelerated approval of andexanet alfa as a reversal agent for all direct Factor Xa inhibitors and the indirect Factor Xa inhibitor, enoxaparin. The FDA did not grant approval for andexenet alfa citing several issues, including insufficient data to support its use in patients requiring reversal of edoxaban or enoxaparin. In response, Portola Pharmaceuticals will shift its current focus, seeking approval for reversal of apixaban and rivaroxaban only. Resubmission to the FDA may occur as soon as the end of 2016.[6]

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Clinical Efficacy: A randomized, double-blind, placebo-controlled trial, with a primary endpoint of change in HbA_{1c} over 13 weeks, evaluated the dose–response relationship of lixisenatide in 542 metformin-treated patients with T2DM.[5] These patients were treated with lixisenatide doses of 5-, 10-, 20-, or 30-mcg once daily, twice daily, or with placebo. Both once and twice daily lixisenatide dosing regimens resulted in an improved HbA_{1c}, despite its short half-life. The most frequent adverse event reported across all treatment groups was nausea, with occurrence more likely with higher treatment doses of lixisenatide. This study concluded that with similar efficacy seen between the once and twice daily regimens, the 20 mcg once daily dose showed the best efficacy-to-tolerability ratio. In a study of 634 patients with T2DM, receiving >1.5 grams per day of metformin, with HbA_{1c} ranging from 7% to 10%, patients were randomized 1:1 to lixisenatide 20 mcg once daily or exenatide 10 mcg twice daily.[6] The primary efficacy endpoint was HbA_{1c} change from baseline to 24 weeks. The least squares mean HbA_{1c} reduction at week 24 was -0.79% for lixisenatide versus -0.96% for exenatide. The noninferiority margin of 0.4% was met, with a mean HbA_{1c} change difference of 0.17% (95% CI, 0.033–0.297). The authors concluded that lixisenatide once daily was noninferior to exenatide twice daily in comparing the mean difference in improvement of HbA_{1c} after 24 weeks.

Safety: The most common adverse events occurring in ≥5% of patients treated with lixisenatide are nausea, vomiting, diarrhea, headache, and dizziness.[2] When combined with other therapies used to treat T2DM (e.g., insulin, metformin, sulfonylureas) rates of hypoglycemia are higher than when used as monotherapy. As with other GLP-1 RAs, lixisenatide use has been associated with pancreatitis.

Dosing and Administration: The recommended starting dose of lixisenatide is 10 mcg subcutaneously once daily for 14 days, increasing to a maintenance dose of 20 mcg once daily starting on Day 15.[2] It will be available as a 50 mcg/mL, 3 mL green pen (14 doses; 10 mcg/dose) and 100 mcg/mL, 3 mL burgundy pen (14 doses; 20 mcg/dose). Lixisenatide is to be administered in either the abdomen, thigh, or upper arm prior to the first meal of the day, compared to later meals, as it has been shown to significantly reduce fasting plasma glucose and postprandial blood glucose at that administration time.

Role in Therapy: Lixisenatide offers another option for patients who could benefit from a GLP-1 RA, but who would prefer once daily dosing. This product has been available since February 2013 in 27 European Union countries for the treatment of T2DM, but anticipated availability of lixisenatide in the United States is currently undetermined.[7,8] Lixisenatide has not been added as a potential option in therapy in either the American Diabetes Association or American Association of Clinical Endocrinologists/ American College of Endocrinology guidelines.[3,9] The Cleveland Clinic Health-System currently does not have any GLP-1 RAs on the Formulary.

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Review of Dantrolene Formulations

By: Mohamed Amar, Pharm.D., BCPS

Background: Malignant hyperthermia (MH) is a rare, life-threatening pharmacogenetic disorder.[1] Its incidence ranges between 1 in 15,000 in children and 1 in 50,000 in adults and occurs more commonly in males than females.[1,2] It is linked to a mutation in the muscle ryanodine receptor isoform 1 (RyR-1) which regulates the release of calcium from the sarcoplasmic reticulum.[2] Patients with MH are predisposed to excessive intramuscular calcium release triggered by exposure to succinylcholine and certain volatile anesthetic agents (e.g.,desflurane, isoflurane).[3] The inability of the muscles to regulate this drug-induced calcium accumulation manifests as persistent muscle contractions and an extreme elevation in core body temperature. Some early signs of MH include tachycardia, tachypnea, masseter muscle rigidity, ventricular dysrhythmias, and hypercarbia.[2] Later symptomology includes hyperthermia, metabolic acidosis, hyperkalemia, and rhabodomyolysis. Delays in the treatment of MH can lead to significant life-threatening complications such as widespread organ failure and disseminated intravascular coagulation (DIC).[3] The mortality associated with MH has been reported to range from 9.5% to 11.7%.[4,5]

Treatment of MH: Some supportive measures to treat MH include hyperventilation with 100% oxygen, hypothermia, correcting metabolic acidosis, correcting hyperkalemia, and lastly diuresis in order to prevent acute kidney injury secondary to myoglobinuria.[2,6] Dantrolene is considered the drug of choice for the treatment of MH.[2,7] It has been estimated that with every 30 minute delay in dantrolene administration the risk of complications increases by a factor of 1.61.[3]

Dantrolene for MH: Dantrolene binds to RyR-1 and interferes with the release of calcium from the sarcoplasmic reticulum, this in turn leads to the relaxation of the skeletal muscles and an eventual reduction in core body temperature.[2] There are three commercially available formulations of parenteral dantrolene sodium: Dantrium® 20 mg (Par Pharmaceutical), Revonto® 20 mg (DSM Pharmaceuticals), and Ryanodex® 250 mg (Eagle Pharmaceuticals).[8-11] All of these products are indicated for the treatment of MH in conjunction with appropriate supportive measures. Ryanodex®, the newest formulation of dantrolene, was approved by the Food and Drug Administration (FDA) in 2014.[8]

Dosage and Administration: The **M**alignant **H**yperthermia **A**ssociation of the **U**nited **S**tates (MHAUS) recommends a 2.5 mg/kg dose of dantrolene be given intravenously for the treatment of MH; this dose may be repeated until symptomology resolves with a maximum cumulative dosage of 10 mg/kg.[6] The MHAUS guidelines do not recommend the use of dantrolene as a prophylactic agent for MH.[12] Although the dose for all dantrolene formulations is identical, Dantrium® and Revonto® require reconstitution of several vials each with 60 mL of bacteriostatic-free sterile water, while Ryanodex® requires reconstitution of just a few vials each with 5 mL of bacteriostatic-free sterile water for injection. Additionally, due to the rapid dissolution rate and small volume of administration, it takes minutes to reconstitute and administer a loading dose of Ryanodex®, whereas it takes over an hour to reconstitute and administer other dantrolene formulations which are difficult to solubilize and require a much greater volume per dose.[3] Precaution should be taken when administering dantrolene, since it is a vesicant with no known antidote for extravasation.[11]

Side effects: The side effects of Ryanodex® are similar to those of other parenteral dantrolene formulations.[8,11] It can cause muscle weakness, manifesting as loss of grip strength and weakness in the legs. It is associated with somnolence and dizziness for up to 48 hours post-dose, particularly when combined with a sedative agent. As a result, patients receiving this medication should not be allowed to ambulate on their own until they regain normal balance and strength. A swallow evaluation is also necessary post-treatment, since dantrolene is associated with dysphagia and choking. Furthermore, dantrolene may cause dyspnea and respiratory muscle weakness, so ventilator settings should be closely monitored in intubated patients.

Major Differences in Formulations: Compared to Dantrium® and Revonto®, Ryanodex® has a shorter preparation time along with a more rapid rate of administration.[3] Ryanodex® has a much lower mannitol content per vial compared to Revonto®/Dantrium®, an amount which is not sufficient to maintain diuresis (125 mg versus 3000 mg per vial, respectively). Ryanodex® has a shorter shelf-life and is approximately twice the cost of Dantrium® and Revonto®. A comparison of the dantrolene formulations is summarized in Table 1.

Table 1: Comparison of Dantrolene Formulations[3,8-11]

	Dantrium®	Revonto®	Ryanodex®
Vial Strength	20 mg	20 mg	250 mg
Diluent Volume per Vial (Bacteriostatic-free Sterile Water)	60 mL	60 mL	5 mL
Concentration of Reconstituted Product	0.33 mg/mL	0.33 mg/mL	50 mg/mL
Mannitol Content per Vial	3000 mg	3000 mg	125 mg
Number of Vials Needed*	35 vials	35 vials	3 vials
Typical Volume to be Administered*	2,100 mL	2,100 mL	14 mL
Rate of Administration	1 hour	1 hour	2 to 3 minutes
Suggested Wholesale Price*	$4,028	$3,192	$8,280
Shelf-life	3 years	3 years	2 years

*Based on a total cumulative maximum dose of 10 mg/kg for a 70 kg patient

Conclusion: Ryanodex® is similar to Dantrium® and Revonto® in that it has the same dosage and adverse effect profile. However, Ryanodex® is much more expensive and has a shorter shelf-life. The benefits of Ryanodex®, in terms of shorter preparation time and a more rapid rate of administration, may exceed any disadvantages (e.g., cost) in the treatment of MH, where delays in therapy can greatly impact clinical outcome. Consequently, all MH carts at CCHS facilities contain Ryanodex®.

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Alvimopan (Entereg®)	Peripheral mu-opioid receptor antagonist	For use in select ERAS protocols	Restricted for use in ERAS protocols for: 1. Radical cystectomies 2. Open bowel resections with primary anastomosis or laparoscopic patients with a high-risk of conversion to open bowel resection 3. Select gynecology surgical procedures (e.g., ovarian cancer debulking) Alvimopan: 1. Can only be ordered from select order sets (i.e., drug file is not on preference list) 2. Can only be dispensed from a certified inpatient hospital pharmacy 3. Cannot be continued upon discharge 4. Has a REMS program due to a black box warning regarding risk of MI with prolonged use 5. Is contraindicated in patients who have been on therapeutic doses of opioids for 7 consecutive days due to increased risk of GI adverse events
Defibrotide (Defitelio®)	Thrombolytic	For treatment of hepatic sinusoidal obstruction syndrome	Restricted to the Department of Bone Marrow Transplant
Ferric Carboxymaltose (Injectafer®)	Iron Salt	Iron Replacement	Restricted to the Department of Hematology and Medical Oncology for outpatient use only
Liposomal Irinotecan (Onivyde®)	Topoisomerase 1 Inhibitor	Treatment of Pancreatic Cancer	Restricted to the Department of Hematology and Medical Oncology for outpatient use only

ERAS=Enhanced Recovery after Surgery GI=Gastrointestinal MI=Myocardial Infarction REMS=Risk Evaluation Mitigation Strategy

Changes to Restrictions in the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change in Restriction**
Dofetilide (Tikosyn®)	Antiarrhythmic Agent Class III	Atrial Fibrillation Atrial Flutter	The Tikosyn® REMS program was withdrawn by the FDA when the product became generic. To ensure continued safe use of this medication, the following restrictions will be in place: 1. All current certified prescribers with the Tikosyn® REMS program will be considered to meet criteria to become a Cleveland Clinic "certified" dofetilide prescriber. 2. Cleveland Clinic will create an internal training program/document for a physician that wants to become a certified prescriber. 3. The initiation of dofetilide is restricted to Cardiologists that are Cleveland Clinic "certified" dofetilide prescribers. 4. The continuation of dofetilide from home is restricted to Cleveland Clinic "certified" dofetilide prescribers.
Intravenous Acetaminophen (Ofirmev®)	Analgesic	Analgesia in post-craniotomy patients who are NPO	Expand restriction to include: Staff Physicians from Neurosurgery and Neurocritical Care for use in post-craniotomy patients who are NPO
Prothrombin Complex Concentrate (KCentra®)	Blood Product Derivative	Warfarin Reversal in Life-Threatening ICH	Removed the Formulary Restriction requirement of Staff only on KCentra® for warfarin reversal in life-threatening ICH

FDA=Food and Drug Administration ICH=Intracranial Hemorrhage NPO=Nothing by Mouth REMS=Risk Evaluation Mitigation Strategy

Therapeutic Interchange in the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Therapeutic Interchange**
Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate (Atripla®)	Antiretroviral	HIV infection	Atripla® tablets will be automatically interchanged **in patients who are unable to swallow whole tablets** to Truvada® (emtricitabine/ tenofovir disoproxil fumarate) tablets plus efavirenz liquid. Rationale: Atripla® tablets may NOT be crushed or split; therefore, to expedite therapy pharmacists may automatically convert orders for Atripla® tablets to the equivalent dose of Truvada® tablets (which may be crushed or split) plus efavirenz liquid in patients who cannot swallow whole tablets. Epic functionality will remind prescribers to change the patients back to Atripla® tablets upon discharge.

HIV=Human Immunodeficiency Virus

Deletion from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal/Comments**
Dinoprostone (Cervidil®) Vaginal Insert	Prostaglandin	Cervical Ripening	Misoprostol tablets can be used for cervical ripening. More cost-effective therapy supported by ACOG.

ACOG=American College of Obstetricians and Gynecologists

Adult CCHS Formulary Changes in Processes and Guidelines			
Drug	**Pharmacologic Class**	**Current Guideline/ Process**	**Modification/Rationale**
Hypertonic Saline 3%	Electrolyte Supplement	Treatment of Hyponatremia **Current Maximum Bolus:** 300 mL **Current Monitoring Frequency:** Every 4 hours	**Modification:** **New Maximum Bolus:** 450 mL **New Monitoring Frequency:** Every 6 hours **Rationale:** To achieve an equivalent dose of 7.5% bolus in mEq of sodium with the 3% hypertonic saline, a 450 mL volume bolus would be needed. There are data to support less frequent monitoring of every 6 hours to allow a more feasible laboratory turn-around time.
PrimaSol®	Renal Replacement Electrolyte Solution	Pharmacists were not permitted to modify PrimaSol® medication orders to correspond to changes in the Procedure Order Section of Epic	**New Process:** Pharmacists may now manage the replenishment request, dispensing process, and alter the medication order rate of administration for PrismaSol® to match the procedure order rate of administration when the two orders are discordant. **Rationale:** This new process will prevent delays in therapy in that the pharmacist will not need to contact a presriber to alter the medication order rate to match the procedure order rate of PrimaSol® when the two are discordant.

Changes with Formulary Products on Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change in Product/Comments**
Dofetilide (Tikosyn®)	Antiarrhythmic Agent Class III	Atrial Fibrillation Atrial Flutter	Cleveland Clinic is converting from brand name dofetilide (Tikosyn®) to generic dofetilide. A free 7-day supply of dofetilide at discharge will no longer be available from the brand manufacturer since Cleveland Clinic is converting to generic. Pharmacy is working on a process to ensure patients will have access to dofetilide at discharge (i.e., either from using Cleveland Clinic Ambulatory Pharmacies or contacting their local pharmacy). Please note: The implementation date of this conversion has not been determined.
Rh Immune Globulin (Rhophylac®)	Immune Globulin	Rh incompatible pregnancies Transfusion of incompatible blood ITP	Rhophylac® has been selected as the Rh immune globulin formulary product for incompatible pregnancies. An Epic Alert will direct all providers to substitute Rhophylac® for Rhogam®. Dosing information for Rhophylac® for all approved indications will be provided in Epic. Rhophylac® can be administered either IM or IV. Dispensing of Rh immune globulin will only come from pharmacy (not the Blood Bank) at all CCHS sites. WinRho® will remain on the Pediatric Formulary for ITP.

IM=Intramuscular ITP=Immune Thromobcytopenia IV=Intravenous

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Defibrotide (Defitelio®)	Thrombolytic	Treatment of hepatic sinusoidal obstruction	Restricted to the Department of Pediatric Bone Marrow Transplant
Palonosetron (Aloxi®)	Selective 5HT-3 Receptor Antagonist	Antiemetic for highly emetic chemotherapy regimens.	Restricted to outpatients receiving highly-emetogenic chemotherapy regimens as outlined by Children's Oncology Group Chemotherapy-Induced Nausea and Vomiting Guidelines