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What's Inside This Issue?

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Initiatives for Standardizations of Oral Compounded Medications

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For many pediatric patients the dosage forms that are commercially available are not always appropriate. Some medications are only available as capsules and tablets, and even some of the oral liquids may contain excipients, such as alcohol, that are not appropriate for pediatric patients. As a result, often times both inpatient and outpatient pharmacies are required to compound oral liquids for pediatric patients.

No mandated national standard for the final concentrations of oral liquid medications exists, leaving pediatric patients vulnerable to high risk of medication errors, especially when transitioning from inpatient to outpatient settings or vice versa.[1] Currently, oral liquid medication concentrations can vary depending on the pharmacy compounding it. Parents may only know the number of mL that their child is receiving which can lead to even more confusion. For instance, if a patient is receiving 5 mL of an oral suspension of metoprolol 12.5 mg/mL as an outpatient and is hospitalized where the hospital compounds 25 mg/mL, the patient could be started on 5 mL of the hospital's oral liquid which would result in a two times overdose.

In a survey sent to 244 Michigan pharmacies, which mainly included outpatient pharmacies, the majority of the pharmacies were compounding fewer than five oral medications per week. The number of concentrations compounded per medication ranged from one to nine, with many of the pharmacies compounding more than three concentrations per medication. 51 errors were identified in Michigan over a 12-month period.[2] Another comprehensive, 80-question survey was sent to twenty-one Children's Hospitals that had >50 beds. In the 12 months prior to the survey, 28% of all inpatient admissions received at least one

compounded oral liquid medication and 6.9% of all doses dispensed were compounded oral medications. These hospitals reported a total 231 drug or drug combinations that were compounded into an oral liquid formulation. Of the formulations, 45% varied in concentration.[3]

Through a grant, the state of Michigan was tasked to standardize oral medication concentrations throughout the entire state. The following state-wide organizations endorsed the collaborative: Michigan Academy of Physician Assistants, Michigan Health & Hospital Association, Michigan Pharmacists Association, Michigan Osteopathic Association, and the Michigan State Medical Society. The initiative consisted of three different phases.[4] The first phase involved surveying pharmacists across the state to better understand the variability of compounded oral liquid medications throughout the state.[1] The second phase involved collaborations with prescribers and pharmacists to determine standard concentrations for a range of medications. The recipes of all of the compounds are supported by published literature. The last phase involved creating a website and other tools to distribute information on the standard concentrations. All of the recipes for the oral liquid medications can be found on their website.[4]

Standardize 4 Safety (S4S) is the first national, interprofessional initiative to standardize medication concentrations in order to reduce errors and improve transitions of care. The Food and Drug Administration, through the Safe Use Initiative, awarded ASHP a three-year contract to develop and implement national standardized concentrations for both intravenous and oral liquid medications. The S4S completed its list of standardized compounded oral liquids including references, which can be found at on the S4S's website.

In order for the S4S initiative to be successful there will need to be adoption of these standardized concentrations in both inpatient and outpatient pharmacies.[5] Like Michigan, Maryland needs to lead the way in oral liquid standardization. I strongly recommend that hospitals adopt the S4S recommendations in an effort to improve medication safety in our state and beyond.

References:

1. Engels MJ, Clarkowski SL, Rood J, Wang B, Wagenknecht LD, Dickinson CJ, Stevenson JG. Standardization of compounding oral liquids for pediatric patients in Michigan. Am J Health Syst Pharm. 2016 Jul 1; 73(13): 981-90.
2. Rood JM, Engels MJ, Clarkowski SL, Wagenknecht LD, Dickinson CJ, Stevenson JG. Variability in compounding of oral liquids for pediatric patients: a patient safety concern. J Am Pharm Assoc (2003). 2014 Jul-Aug; 54(4) 383-9.
3. Lugo R, Cash J, Trimby R, Ward R, Spielberg S. A survey of children's hospitals on the use of extemporaneous liquid formulations in the inpatient setting. JPPT. 2009 Jul-Sep; 14(3): 154-192.
4. University of Michigan College of Pharmacy. State-Wide Initiative to Standardize the Compounding of Oral Liquids in Pediatrics (2018). http://mipedscompounds.org/ (accessed 2018 Aug 14).
5. American Society of Health-System Pharmacists. Standardize 4 Safety Initiative (2018). https://www.ashp.org/Pharmacy-Practice/Standardize-4-Safety-Initiative (accessed 2018 Aug 14).

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Pharmacy Technician Corner: A Day in the Life…

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Three years ago the pharmacy at the University of Maryland Medical Center (UMMC) implemented a pharmacy technician competency progression and compensation adjustment. The hospital's leadership demonstrated their support of the pharmacy department and appreciation for the technician role by approving the comprehensive compensation review to design a clear path for training and specialization. The analysis took into consideration years of experience as a technician and the current competency in our hospital. We divided staff into four competency levels based on the level of supervision in the area, pharmacy area, and patient population served. A majority of the technicians received a monetary hourly rate increase as a result of this market analysis and progression adjustment.

In addition to the career ladder, there have been several advanced practice technician positions created at UMMC. Technicians selected for advanced roles are evaluated based on their previous experience, ability to work independently, and technology and education background. The technicians in these visible roles are great communicators and can work effectively with various disciplines. Below is a short description of some of the specialized roles performed by pharmacy technicians at UMMC in their own words.

A Day in the Life of an Advanced Practice Technician (340B Analyst) by Shalini Balakrishnan

I began my career in pharmacy as a technician at UMMC. This gave me great insight into the inner workings of a hospital and its workflow and detailed knowledge of specialty drugs that I would not have come by in a retail setting. After 6 years of experience working in a pediatric pharmacy, as well as a cancer center pharmacy, I was promoted to a role as a 340B Analyst within my organization.

The 340B drug discount program is a US federal government program that requires drug manufacturers to provide outpatient drugs to eligible healthcare organizations and covered entities at significantly reduced prices. The purpose of the program is to allow safety-net hospitals to stretch resources to help manage rising prescription drug costs. I was able to use my background and knowledge of drugs utilized in specific settings, as well as pharmacy workflows, in this new role to perform data management, reporting, and analytics to maintain program compliance for the institution's 340B drug purchasing program.

On any given day I complete daily, weekly, and monthly monitoring processes by running reports and performing analytics to measure and manage program compliance. I am responsible for completing monthly self-audits of EMR/drug utilization data and third party applications, and implementing action plans and procedures that result from these audits. For this role I need to be proficient with Microsoft Excel and Word, as well as Epic EMR reporting tools, for analytical reporting needs for operational and clinical decision support. There are numerous opportunities within my role to learn more about how money moves through a hospital as well as the ability to use data analytics and informatics to enable better patient care.

A Day in the Life of a Business Operations Supervisor by Joshua Denford

A typical day in this role has a range of duties both challenging and impactful in new ways that I hadn't been previously responsible for as a lead technician. My time as a technician gave me a depth of knowledge about

our pharmacy operations and provided an intimate understanding of the dispensing data sets during any analysis. It also gave me an opportunity to practice efficient operational procedures. A four year degree prepared me to excel in a setting rooted in analytics, mathematics, or numerical problem solving and reasoning. My current role has expanded all of these traits and exposed me to new ones that are more technical than I would've encounter in a technician role.

A large portion of my role involves managing our 340B program. Such a program requires constant auditing of 340B eligible dispenses. Different audits may target specific aspects of patient, doctor, insurance, drug, financials, purchasing, or other kinds of data which may all impact the 340B program. A broad set of Microsoft Excel skills, as well as an understanding of retail and hospital outpatient setting operations, are required to audit these areas. The 340B regulation has changed in the last few years and new changes are always on the horizon, which requires new operational procedures to be implemented to ensure compliance with the program.

New financial software management systems are being implemented across our system and I assist by managing the implementation and management of the software and reporting applications. The rest of my role includes evaluating retail pharmacy analytics, providing decision support to senior leadership, working on financial projections for new business development, and assisting with pharmacy operations. I really enjoy being in this role and encountering and overcoming new challenges. I look forward to continuing to expand my skill set which started with what I learned as a pharmacy technician.

A Day in the Life of a Diversion Analyst by Heekyung Choi

The surveillance program for controlled substances is exceptionally important for patient safety, as well as staff safety in our work environment. Since employees have access to controlled substances to perform their duties, all transactions should be diligently monitored for accountability. This position requires a strong ability for data interpretation and basic knowledge of Microsoft Excel. Some of the duties assigned daily are: monitoring/investigating all automated dispensing cabinet (Pyxis) discrepancies, auditing outliers based on controlled substance transactions, reviewing medication override transactions, and many other activities within UMMC revolving around controlled substances.

Every day I email findings to managers and follow up with specific requests. In my role I interact with nurses and providers and attend multidisciplinary meetings. I train nurse managers to review reports and we work together to update controlled substances policies and procedures. I enjoy the variety of tasks and that each day can bring a challenge. Having experience in the hospital as a pharmacy technician helped me understand the workflow, possible breakdowns in procedures, and how to identify non-compliance.

New Drug Update: Daratumumab for Multiple Myeloma

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In November 2015, FDA initially approved daratumumab (Darzalex®) as a treatment option in Multiple Myeloma (MM) patients whose cancer progressed after receiving at least three prior treatment regimens using standard combination therapies.[1] A year later, It was also approved for combination with

immunomodulatory agents (IMiD's) and proteasome inhibitors (PI's) in patients with relapsed and refractory MM after IMiD's or PI's. [1,3]

Daratumumab is a human IgG1 kappa monoclonal antibody, which specifically targets CD38, a type II transmembrane glycoprotein that is highly and uniformly expressed on multiple myeloma cells. [3, 4] The cytostatic and cytotoxic abilities of daratumumab interrupt signaling by binding to the target directly and, in addition, activate potent cytotoxic immune effector functions in mechanisms known as antibody dependent cellular cytotoxicity and complement-dependent cytotoxicity respectively. [3]

The FDA approved a new indication and combination for Daratumumab (Darzalex®) in May 2018 in combination with bortezomib, melphalan, and prednisone (DVMP) in newly diagnosed MM patients ineligible for autologous stem cell transplant. [2, 5]

ALCYONE a phase-3 randomized trial was initiated in patients' ≥18yrs including 706 newly diagnosed MM patients ineligible for autologous stem cell transplant. This evaluated VMP (control group) against DVMP (intervention group). [2] Patients received daratumumab 16 mg/kg as intravenous infusion in 6 week (42 day) cycles, once weekly in Cycle 1 and then once every 3 weeks, in Cycle 2 to 9, and once every 4 weeks thereafter until documented progression, unacceptable toxicity, or study end. The bortezomib dose was 1.3mg/m^2 of body surface area twice weekly on weeks 1, 2, 4 and 5 in cycle-1, and then once weekly in weeks 1, 2, 4 and 5 from cycle 2 through 9. Oral melphalan and prednisone were dosed at 9mg/m^2 and 60mg/m^2 respectively given once daily on days 1 through 4 of each cycle. An hour or less prior to daratumumab infusion, the intervention group received dexamethasone 20mg IV or oral on D1 and prednisone for the rest of D2-4 of every cycle. Normal saline hydration, antipyretics, and antihistamines were administered as premedication to prevent infusion reactions. [5]

ALCYONE showed a significant 18-month progression free survival at a rate of 71.6% (95% CI, 65.5 to 76.8) in daratumumab group and 50.2% (95% CI, 43.2 to 56.7) in the control group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.38 to 0.65; P<0.001). The median overall survival was not yet reached on either arm of the trial.

The most reported common adverse events of grade 3 or 4 were hematologic; neutropenia 39%/38.7%, thrombocytopenia 34.4%/37.6%, anemia 15.9%/19.8% in intervention versus control respectively. Infections comprising of upper respiratory tract infection and pneumonia were reportedly higher in the daratumumab group at 23.1% compared to 14.7% in control group, which increased treatment discontinuation. Any infusion-related reactions occurred in 27.7% of the patients on daratumumab. GI, arthralgia, and back pain had reported incidence of ≥ 20%.

Based on ALCYONE, patients potentially have a longer disease free period with addition of daratumumab to VMP.[2] The new approval is potentially suitable only in addition to VMP for newly diagnosed MM patients ineligible for autologous stem cell transplant. However, this use has not been compared to other standard of care options at this time.

References:

1. Daratumumab (DARZALEX). Fda.gov. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm530249.htm. Published 2018. Accessed July 7, 2018.

2. Mateos M, Dimopoulos M, Cavo M et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. *New England Journal of Medicine*. 2018;378(6):518-528.
3. Sanchez L, Wang Y, Siegel D, Wang M. Daratumumab: a first-in-class CD38 monoclonal antibody for the treatment of multiple myeloma. *J Hematol Oncol*. 2016;9(1).
4. Nijhof I, Groen R, Noort W et al. Preclinical Evidence for the Therapeutic Potential of CD38-Targeted Immuno-Chemotherapy in Multiple Myeloma Patients Refractory to Lenalidomide and Bortezomib. *Clinical Cancer Research*. 2014; 21(12):2802-2810.
5. Accessdata.fda.gov. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761036s014lbl.pdf. Published 2018. Accessed July 7, 2018.

New Drug Update: Segesterone Acetate/Ethinyl Estradiol Vaginal System (Annovera™)

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Combination hormonal contraceptives (CHCs), such as estrogen and progestin are approved by the Food and Drug Administration (FDA) for the treatment of acne vulgaris and in the prevention of pregnancy. Estrogen and progestin prevent pregnancy by suppressing follicle stimulating hormone (FSH) and luteinizing hormone (LH), subsequently inhibiting ovulation, altering the structure of the endometrium, and increasing the thickness of cervical mucus.[1] Ethinyl estradiol (EE) is a widely used estrogen in contraceptives. Segesterone acetate (SA), or Nestorone (NES), is a new nonandrogenic progestin that is being combined with ethinyl estradiol, with an FDA approved indication to prevent pregnancy.[2]

TherapeuticsMD, Inc., in partnership with Allergan and Population Council, have developed Annovera™ (segesterone acetate/ethinyl estradiol vaginal system), which was just approved by the FDA on August 10th, 2018.[3] This is the second estrogen/progestin CHC ring on the market, indicated to prevent pregnancy in females of reproductive potential. The first CHC ring approved by the FDA was NuvaRing® (ethinyl estradiol/etonogestrel (ETO)) in 2001.[1-3] What sets Annovera™ apart from NuvaRing® is that it is the first long-acting contraceptive that is reversible, patient-controlled, procedure-free, reusable, and the first and only birth control that has been approved as a vaginal system. This flexible system can be used for one year, and is inserted into the vagina for a continuous three weeks, releasing on average 0.15 mg/day of SA and 0.013 mg/day of EE, and then removed for one week. This process is repeated every four weeks for one year (thirteen 28-day menstrual cycles). Annovera™ is washed and stored in its compact case during the seven days it is not in use. Refrigeration is not required and it can withstand temperatures up to 30°C (86°F).[3-5]

The safety and efficacy of Annovera™ contraceptive vaginal ring (CVR) were evaluated from two 13-cycle (over 12 months), phase 3, open-label trials in 2,308 women aged 18 to 40 years at 27 different sites throughout the United States and internationally. In these interventional studies, patients were given 150 µg of Nestorone and 15 µg of ethinyl estradiol (150/15 NES/EE CVR), administered via vaginal ring, with a regimen of 21/7-days in/out schedule for 12 months.[2-3]

At about 50% enrollment, women with a body mass index (BMI) > 29 kg/m^2 were discontinued from the trials due to two serious adverse reactions of venous thromboembolism (VTE) events, defined as deep venous thrombosis, cerebral vein thrombosis, and pulmonary embolism. The use of Annovera™ is inadvisable in this patient population, but not contraindicated. Nuvaring® does not have this same limitation of use. Thrombotic disorders and other vascular problems are also a warning and precaution on the labeling, which is

common with hormonal contraceptives. A Black Box Warning (BBW) of cigarette smoking and serious cardiovascular events (another common occurrence in hormonal contraceptives) is also included in its label. Something to note is that higher body weight leads to a decrease in systemic exposure of SA and EE.[2-5]

Serious adverse reactions that occurred in ≥2 subjects included VTEs, psychiatric events, drug hypersensitivity reactions, and spontaneous abortions. The top three most common adverse reactions reported by ≥ 5% of patients (n=2,308) using Annovera™ were headache, including migraine (38.6%), nausea/vomiting (25.0%), and vulvovaginal mycotic infection/vaginal candidiasis (14.5%). Metrorrhagia/menstrual disorder also occurred in 7.5% of patients. These four adverse reactions led to discontinuation in ≥ 1% of patients using Annovera™. Discontinuation due to expulsion of the ring occurred in 1.4% of subjects.[3]

Annovera™ was shown to be 97.3% effective at preventing pregnancy, making it the most effective, patient-controlled birth control.[5] The Pearl Index (PI), evaluating the pregnancy rate, from pooled data of 2,111 females aged ≤ 35 years, was 2.98 (95% CI [2.13,4.06]) per 100 woman-years (WY).[3,5] An acceptability study was administered to 1,036 women enrolled in one-year phase 3 trial. Acceptability was measured in four domains as the satisfaction of ease of use, side effects, expulsions/feelings of the vaginal ring, and sexual activity. It was hypothesized that these domains, developed based on reviews of previous literature, would be factors in patient satisfaction and subsequent adherence and continuation. Annovera™ had an overall patient satisfaction rate of 89% (in 806 women) and led to higher adherence [OR 2.6 (1.3,5.2)] and continuation [OR 5.5 (3.5,8.4)] compared with dissatisfied women.[6]

Annovera™ has been classified as a new chemical entity (NCE), which although often used interchangeably with new molecular entity (NME), is different. The Code of Federal Regulations (CFR), title 21, section 314.108(a) defines NCE as a drug that contains no active moiety that has been approved by the FDA in any other application submitted under section 505(b) of Food, Drug, and Cosmetic (FD&C) Act. Comparatively, an NME has been previously approved by the FDA or marketed in the United States. Having attained the classification as an NME, TherapeuticsMD has 5 years of market exclusivity under the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments).[7-8] As a new drug, it can be expected that the Affordable Care Act (ACA) will be required to cover this contraceptive for patients with no out-of-pocket costs.[5] TherapeuticsMD has also voiced they will offer reduced pricing for family-planning clinics servicing lower-income families.

The Centers for Disease Control and Prevention (CDC) reports that unintended pregnancies result from not using contraception, incorrect or inconsistent use of various methods. Despite declines in unintended pregnancies over the years, unintended pregnancies remain highest among low-income, young females who are cohabitating.[8-9] Annovera™ could help decrease unintended pregnancies and improve adherence to hormonal contraceptives, while also increasing the use of hormonal contraceptives.

References:

1. Nuvaring® [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2018.
2. Safety and Efficacy of a Contraceptive Vaginal Ring Delivering Nestorone® and Ethinyl Estradiol. Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT00263341. Accessed August 27, 2018.
3. Annovera™ [package insert]. New York, NY: Population Council; 2018
4. U.S. Food & Drug Administration. Press Announcements – FDA approves new vaginal ring for one year of birth control. U.S. Food and Drug Administration Home Page.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm616541.htm. Accessed August 27, 2018.
5. TherapeuticsMD Announces FDA Approval of ANNOVERA™ (Segesterone Acetate/Ethinyl Estradiol Vaginal System) for Birth Control. TherapeuticsMD Inc. https://ir.therapeuticsmd.com/news-releases/news-release-details/therapeuticsmd-announces-fda-approval-annoveratm-segesterone. Accessed August 27, 2018.
6. Merkatz RB, Plagianos M, Hoskin E, Cooney M, Hewett PC, Mensch BS. Acceptability of the nestorone®/ethinyl estradiol contraceptive vaginal ring: development of a model; implications for introduction. Contraception. 2014;90(5):514-521. doi:10.1016/j.contraception.2014.05.015.
7. Policy and Procedures Office of Pharmaceutical Quality NDA Classification Codes. FDA.gov. https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesproceedures/ucm470773.pdf. Published November 4, 2015. Accessed August 27, 2018.
8. New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products: Guidance for Industry. FDA.gov. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm386685.pdf. Published October 2014. Accessed August 27, 2018.
9. Unintended Pregnancy Prevention. Centers for Disease Control and Prevention. https://www.cdc.gov/reproductivehealth/contraception/unintendedpregnancy/index.htm. Published December 23, 2016. Accessed August 27, 2018.
10. Declines in Unintended Pregnancy in the United States, 2008–2011 | NEJM. New England Journal of Medicine. https://www.nejm.org/doi/full/10.1056/NEJMsa1506575. Accessed August 27, 2018.

New Drug Update: Andexanet Alfa (Andexxa®) for Factor Xa Reversal

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In May 2018, the Food and Drug Administration (FDA) approved a novel medication, andexanet alfa (Andexxa), as an antidote of factor Xa inhibitors apixaban (Eliquis) and rivaroxaban (Xarelto).[1] This is the second antidote approved by the FDA to reverse the effect of direct oral anticoagulants (DOACs) and the first to reverse the effect of factor Xa inhibitors. Andexanet alfa is a genetically modified variant of human factor Xa and works by acting as a decoy, binding to factor Xa inhibitors and neutralizing the anticoagulation effect.[1,2] This mechanism allows andexanet alfa to reverse all direct (apixaban, edoxaban, rivaroxaban and betrixaban) and indirect (fondaparinux and enoxaparin) factor Xa inhibitors, although only rivaroxaban and apixaban are part of the FDA-approved indication.[3]

The FDA granted accelerated approval to andexanet alfa based on the safety and efficacy results from two randomized clinical trials, ANNEXA-A and ANNEXA-R. The principle objective of both of these trials was to evaluate the ability of andexanet alfa to safely reverse the anticoagulant effects of apixaban and rivaroxaban, respectively.[2,4] These trials were published in the New England Journal of Medicine (NEJM) in 2015.[1,2,4] The primary endpoint of both studies was the percent change in anti-factor Xa activity from baseline.[2,4] These trials concluded that andexanet alfa effectively reverses the anticoagulant effects of factor Xa inhibitors apixaban and rivaroxaban within minutes of administration. The results of both trials were statistically significant with a p value of $p<0.001$. No serious adverse or thrombotic events were reported for either trial.[2,4]

Under the ANNEXA-A study, 48 patients were given 5 mg apixaban orally twice a day for 3.5 days to achieve steady state plasma levels. The randomization ratio of andexanet alfa to placebo was 3:1. On day 4, at 3 hours after the last dose of apixaban, andexanet alfa was administered as a 400-mg IV bolus (30 mg/min) for part 1

of the study. For part 2, the 400-mg IV bolus was followed by a continuous infusion of 4 mg/min for 2 hours (total 480 mg). The results of this clinical trial favored andexanet alfa against placebo as anti-factor Xa activity was reduced rapidly after the administration of a bolus dose of andexanet alfa. For part 1, the anti-factor Xa activity was reduced by 94% among those who received an andexanet alfa bolus (24 participants) as compared with 21% among those who received placebo (9 participants). The unbound apixaban concentration was reduced by 9.3 ng/mL with the andexanet alfa bolus, and with the placebo, the concentration of apixaban was decreased by 1.9 ng/mL. Thrombin generation was fully restored in 100% with andexanet alfa versus 11% with placebo within 2 to 5 minutes. The outcomes were consistent in part 2 in which andexanet alfa was administered as a bolus followed by a continuous 2 hour infusion. The reduction of anti-factor Xa from baseline was 92% with andexanet alfa and 33% with placebo.[2,4]

Under the ANNEXA-R study, 53 participants received rivaroxaban 20 mg orally once daily for 4 days. The randomization ratio of andexanet alfa to placebo was 2:1. On day 4 of receiving rivaroxaban, at 4 hours after the last dose, andexanet alfa was administered as an 800-mg IV bolus (30 mg/minute) for part 1. For part 2, the 800-mg IV bolus was followed by a continuous infusion of 8 mg/minute for 2 hours (total 960 mg). Relative to the dose of andexanet alfa in the ANNEXA-A study, the dose of andexanet alfa is higher in ANNEXA-R because of the higher initial maximum plasma concentration and larger volume of distribution of rivaroxaban. For part 1, the anti-factor Xa activity was reduced by 92% among those who received an andexanet alfa bolus (27 participants) as compared with 18% among those who received placebo (14 participants) and unbound rivaroxaban concentration was reduced by 23.4 ng/mL versus 4.2 ng/mL in the andexanet alfa group and placebo group, respectively. As for part 2, andexanet alfa reduced anti-factor Xa activity by 97% among those who received an andexanet alfa bolus followed by a continuous infusion as compared to a 45% reduction among those who received placebo. Thrombin generation was fully restored in 96% versus 7% of the participants. Additionally, the effects were sustained when andexanet alfa was administered as a bolus followed by an infusion.[2,4]

The September 2016 study, ANNEXA-4 (also published in NEJM) evaluated the effect of andexanet alfa in patients with acute major bleeding. This severity was defined as potentially life-threatening acute overt bleeding with signs or symptoms of hemodynamic compromise (i.e., severe hypotension, poor skin perfusion, mental confusion, or low cardiac output that could not otherwise be explained). Patients in the study also had to have a decrease in hemoglobin $\geq$ 2 g/dL or hemoglobin level $\leq$ 8 g/dL (in the absence of a baseline level), acute symptomatic bleeding in a critical area or organ, and anti-factor Xa activity $\geq$ 75 ng/mL for the efficacy analysis. These patients received one of the four factor Xa inhibitors: apixaban, rivaroxaban, edoxaban or enoxaparin.[2,5] In this study, 67 patients with acute major bleeding within 18 hours after the administration of a factor Xa inhibitor received andexanet alfa bolus followed by a two hour infusion. Patients who had taken apixaban or rivaroxaban > 7 hours before andexanet alfa received a bolus dose of 400 mg followed by an infusion dose of 480 mg. Patients who had taken enoxaparin, edoxaban or rivaroxaban dose $\leq$ 7 hours before administration or at an unknown time received an andexanet alfa bolus dose of 800 mg followed by an infusion dose of 960 mg.[2,5,6]

The two primary outcomes were the percent change in the anti-factor Xa activity and the rate of excellent or good hemostatic efficacy 12 hours after the andexanet alfa infusion. For patients who received rivaroxaban, the median value for anti-factor Xa activity fell from 277.0 ng/mL (baseline) to 16.8 ng/mL (89% decrease) at the end of the bolus administration, whereas the median value for anti-factor Xa activity was 30.6 ng/mL at

the end of the two hour infusion (86% decrease from baseline). Similar results can be seen in the apixaban group where the median value for anti-factor Xa activity reduced from 149.7 ng/mL at baseline to 10.3 ng/mL at the end of the bolus dose (93% decrease). The median value for anti-factor Xa activity at the end of the infusion dose was 12.5 ng/mL (92% decrease from baseline). Out of 47 patients analyzed for hemostatic efficacy, 37 patients categorized as either excellent or good 12 hours post-andexanet alfa infusion (31 patients excellent, 7 patients good).[2,5,6]Although the ANNEXA-A and ANNEXA-R trials were conducted in healthy volunteers, the results of those studies were consistent with the results of the ANNEXA-4 trial. Additionally, this study's andexanet alfa algorithm is now used to support the use of andexanet alfa in patients with acute major bleeding who require urgent reversal.

Andexanet alfa is supplied as 100 mg single use vial in IV formulation that requires reconstitution with 10 mL of sterile water for injection.[1,2] Portola Pharmaceuticals plans to release a 200 mg "second generation" product in March of 2019. The Low Dose (400 mg bolus followed by 480 mg infusion) will cost around $24,700 per dose as compared to the High Dose (800 mg bolus followed by 960 mg infusion) which will cost around $49,500 per dose.

The drug has a black box warning for risk of thromboembolic, ischemic and cardiac events, including sudden death in patients treated with andexanet alfa. Other common adverse reactions that can be caused by andexanet alfa include urinary tract infection, pneumonia and infusion related reactions.[1,2]

References:

1. Andexxa-An Antidote for Apixaban and Rivaroxaban [Review]. (2018). JAMA,320(4).
2. Andexxa [package insert]. South San Francisco, CA: Portola Pharmaceuticals Inc; 2017.
3. Heo, Y.-A. (2018). Andexanet Alfa: First Global Approval. Drugs, 78(10), 1049–1055.
4. Siegal, D. M., Curnutte, J. T., Connolly, S. J., Lu, G., Conley, P. B., & Wiens, B. L. (2015). Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. JAMA,373, 2413-2424.
5. Connolly, S. J., Milling, T. J., & Eikelboom, J. W. et. Al (2016). Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. New England Journal of Medicine,375(12), 1131-1141.
6. Connolly, S. J., Milling, T. J., & Eikelboom, J. W. et. Al (2016). Andexanet alfa in Factor Xa Inhibitor-Associated Acute Major Bleeding [PowerPoint slides]. Presented at American College of Cardiology's 67th Annual Scientific Session & Expo.

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Submit articles for publication in the Spring Edition of Pharmascript by March 15, 2019