Written testimony of Janet Long, Director of Research, US Hereditary Angioedema Association to the Oregon Pharmaceutical and Therapeutics Committee on March 21, 2019 Salem, OR

Dear Chair and members of the Pharmaceutical and Therapeutics Committee, my name is Janet Long.

I am a patient with severe HAE and am privileged to serve our patient community as Research Director for the US Hereditary Angioedema Association (HAEA)—a 5600 member non-profit advocacy and research organization, founded and staffed by HAE patients and care givers.

HAE is a disabling and potentially fatal disorder that causes attacks of massive swelling in various body parts that can last from 3 to 5 days. I can tell you from personal experience that swelling that occurs in hands, feet, face, and abdomen is extremely painful and disabling. But the biggest fear is laryngeal swelling, because it can cause death by suffocation. Peer reviewed burden of illness studies and other research reveal that inadequately treated HAE causes severe disability, and the historical *mortality rate* for untreated patients is over 40 percent.

Several years ago, the HAEA's Medical Advisory Board - a distinguished group of expert physician/scientists - published "Recommendations on the Management of HAE" in a prestigious medical journal.

I am here to ask that this review of Medicaid Preferred Drugs for HAE include careful consideration of the Medical Advisory Board 's HAE Management Recommendations. This document offers a set of principles and practices to **ensure efficient and cost-effective use** of the FDA-approved HAE therapies available to treat this disabling and potentially life-threatening disease.

I would like to highlight a few key points from the Recommendations:

- 1) Because not all patients respond the same to all medications, an expert physician must work with each patient to determine the optimal treatment.
    - For that reason, we urge Oregon Medicaid to continue allowing access to all medicines FDA-approved to treat HAE.
- 2) For some patients, on-demand treatment alone is sufficient; for other patients, prophylactic treatment is indicated as first-line treatment together with on-demand treatment for breakthrough attacks.
- 3) Since life threatening laryngeal edema can occur at any time, patients should have access to at least 2 standard doses of an FDA-approved medicine for on-demand treatment of acute HAE attacks.
- And lastly, because of the disfiguring and painful effects of swelling, all attacks should be considered for treatment as soon as the symptoms are clearly recognized.

In closing, I would like to stress again that **first** key point made in the Recommendations, that not all patients respond the same to all HAE medications, so an expert physician must work with each patient to determine the optimal therapy for them. Therefore, we again kindly ask that Oregon Medicaid allow access to **all** FDA-approved therapies (including on formulary) to treat HAE…the lives of all HAE patients in Oregon depend on it.

Thank you

The US HAE Association www.haea.org
10560 Main St. Suite PS40 | Fairfax City, VA 22030 | phone 866 798 5598 | fax 508 437 0303

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King of Prussia, PA 19406
484-751-4920
484-751-4995 fax

March 15, 2019

P&T Committee Members
OSU College of Pharmacy - Drug Use Research & Management @ OHA Health Systems Division
500 Summer Street NE, E35
Salem, OR 97301-1079
osupharm.di@oregonstate.edu
Phone: 503-947-5220

Dear P&T Committee Members,

I am writing to you on behalf of Paratek Pharmaceuticals, Inc. regarding the report you authored titled: "*Drug Class Update with New Drug Evaluation: Oral Tetracyclines*". I understand this report was prepared in advance of the Oregon State Medicaid tetracycline class review later this month. I want to take this opportunity to thank you for preparing this report that supports and seeks to improve appropriate antibiotic use. Medication management standards, guidelines and formularies that support appropriate antibiotic use and drive the adoption of those standards, can improve the quality of care and clinical outcomes provided to Medicaid beneficiaries.

The appropriate use of antimicrobials is one of the biggest public health threats facing the United States, and a critical element in the battle against Antimicrobial Resistance (AMR) is reducing inappropriate use of antimicrobials. We think there are common sense approaches to address these public health challenges which include provider choice of medications that meet the specific needs and conditions of each patient. Suboptimal therapy of older antibiotics accounts for roughly 23,000 deaths and over $20 billion in unnecessary costs in the United States each year. The increase of antibiotic resistance continues to drive the need for new, well tolerated effective therapies. While the tetracyclines once may have represented a mainstay of broad-spectrum antibiotics for many years, the increasing incidence of bacterial resistance has relegated the older oral tetracyclines to a very limited role for treating common infectious diseases. It is more critical than ever that optimal antibiotic use be required to limit the unintended adverse effects of inappropriate prescribing.

In preparation for the Medicaid meeting on March 21, 2019, I kindly ask for your review of the summary included below, describing the unmet need for new antibiotics to treat patients with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI). NUZYRA™ (omadacycline) provides an alternative once-daily oral and IV monotherapy option for patients when resistant pathogens are suspected and has been shown to effectively address the patients that may not be appropriately treated by existing generic options. Aside from suspected resistant pathogens, other reasons that generic options might not be suitable, include patients with allergies to either penicillin's or beta-lactams. In addition, patients with renal or hepatic impairment, or the physician has safety concerns with drug-drug interactions limit the use of vancomycin and linezolid.

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Finally, other alternative antibiotics such as fluoroquinolones have had increasing safety warnings that limit their use. We strongly believe that the appropriate use of new antibiotics, such as NUZYRA™, play a critical role in the treatment of conditions such as CABP and ABSSSI.

Once again, I appreciate you taking the time to consider our position and the opportunity to include additional information in the decision-making process of the selection of antibiotics for Medicaid beneficiaries.

Please feel free to reach out to me directly with any questions.

Sincerely,

Evan Loh, MD
President, Chief Operating Officer & Chief Medical Officer
Paratek Pharmaceuticals, Inc
phone: 484.751.4999
email: Evan.Loh@paratekpharma.com

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paratekpharma.com
1000 First Ave, Suite 200
King of Prussia, PA 19406
484-751-4920
484-751-4995 fax

SUMMARY FOR NUZYRA™ (omadacycline)

Unmet Need

The emergence and spread of antibiotic-resistant organisms continues to outpace the development of antibiotics to treat these pathogens.[1] Infections caused by antibiotic-resistant organisms increase morbidity and mortality in patients and increases the resource consumption for healthcare systems in the U.S.[2] The Centers for Disease Control and Prevention has estimated that 2 million patients per year have infections due to drug-resistant bacteria, resulting in 23,000 deaths annually in the United States (US).[2] Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pneumoniae* (*S. pneumoniae*, or pneumococcus), known to be leading causes of bacterial skin and community-acquired pneumonia infections, have been classified as serious threats by the CDC.[2]

CABP and ABSSSI are serious diseases associated with substantial morbidity and increased healthcare costs.[3-8] Together with influenza, community acquired pneumonia is currently the eighth leading cause of death in the US.[9] Bacterial resistance, including multi-drug resistance, have presented a therapeutic challenge to clinicians with respect to the selection of appropriate empiric antibiotic therapies, especially as bacterial resistance to the current guideline-recommended antibiotics has increased.[10] In addition, safety concerns related to certain classes of antibiotics, as well as availability of only an IV formulation are additional prescribing considerations.[11,12]

Appropriate, timely, and effective antibiotic therapy are among the most important factors in ensuring successful treatment of CABP and ABSSSI.[13-15] It is beneficial for treating physicians to have different antibacterial options that can provide timely, appropriate therapy against drug-resistant strains. Because of the diversity of the patient populations, antibiotic allergies, patient comorbidities, and drug-drug interactions, it is imperative to have antibacterial drugs with different safety and tolerability profiles to provide physicians with options for patient care.

Omadacycline was approved by FDA on October 2, 2018 for the following indications as per the approved US Prescribing Information:

INDICATIONS AND USAGE[16]

Community-Acquired Bacterial Pneumonia (CABP)

NUZYRA is indicated for the treatment of adult patients with CABP caused by the following susceptible microorganisms: *Streptococcus pneumoniae*, *Staphylococcus aureus* (methicillin-susceptible isolates), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae, Legionella pneumophila*, *Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae*.

Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

NUZYRA is indicated for the treatment of adult patients with ABSSSI caused by the following susceptible microorganisms*: Staphylococcus aureus* (methicillin susceptible and resistant isolates), *Staphylococcus lugdunensis*, *Streptococcus pyogenes, Streptococcus anginosus* grp. (includes *S. anginosus*, *S.*

intermedius, and *S. constellatus*), *Enterococcus faecalis*, *Enterobacter cloacae,* and *Klebsiella pneumoniae.*

Usage
To reduce the development of drug-resistant bacteria and maintain the effectiveness of NUZYRA and other antibacterial drugs, NUZYRA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

Contraindications
NUZYRA is contraindicated in patients with known hypersensitivity to omadacycline or tetracycline class antibacterial drugs, or to any of the excipients.

About NUZYRA (omadacycline)
Omadacycline is an aminomethylcycline antibacterial, within the tetracycline class, that was designed to overcome the most common mechanisms of tetracycline resistance. It is structurally distinct from other tetracyclines by specific modifications at the C-7 and C-9 positions.[17] *In vivo* and *in vitro* studies have shown, that omadacycline retains activity against bacterial strains expressing either efflux pump or ribosomal mechanisms of tetracycline resistance that impact older tetracyclines.[18]

Omadacycline has clinical activity against select gram positive, gram negative and atypical pathogens, including *S. pneumoniae* and *H. influenzae* commonly observed in CABP, as well as MRSA a leading cause of ABSSSI.[18-22] The *in vitro* activity of omadacycline has been assessed in large global surveillance studies of clinical isolates and the spectrum of activity includes Gram-positive, Gram-negative, aerobic, anaerobic, and atypical bacteria, including drug resistant strains.[23,24] The clinical significance of this *in vitro* data is unknown.

Clinical Efficacy for Omadacycline
While contemporary randomized, active-comparator clinical data are limited for the historical tetracyclines in the setting of ABSSSI and CABP, omadacycline has been studied in a comprehensive and robust clinical development program of 27 studies completed to date. In this development program, 1,947 patients were exposed to omadacycline, including 1,073 patients exposed to omadacycline in the pivotal Phase 3 studies for CABP and ABSSSI.[18-21]
In two pivotal Phase 3 studies in patients with ABSSSI, omadacycline was determined to be non-inferior to the linezolid, an IDSA Guideline recommended agent. Clinical success rates were high (≥85%) at the early clinical response (ECR) primary endpoint assessment, as well as at the investigator-assessed post-therapy evaluation (PTE) secondary endpoint, thus demonstrating early and sustained efficacy through the PTE endpoint.[20-22]

In the pivotal Phase 3 study for CABP, omadacycline was determined to be non-inferior to the gold standard comparator moxifloxacin. Clinical success rates were high (88%) at the ECR primary endpoint assessment as well as at the later investigator-assessed PTE secondary endpoint, again demonstrating early and sustained efficacy through the PTE endpoint. Additional subgroup, and symptom-based analyses demonstrate the robustness of the primary efficacy assessment. Similar rates of clinical success were observed at the ECR and PTE assessment between PORT Risk Class and treatment groups.[19]

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Key Pharmacokinetics

Key pharmacokinetic properties of omadacycline include 34.5% oral bioavailability following a single 300 mg dose, a 17-hour half-life, and low protein (~20%) binding.[25,26] In addition, omadacycline has a high volume of distribution, including high and sustained concentrations in human pulmonary tissues.[26,27] Once daily 100 mg IV and 300 mg oral formulation provide similar drug exposures.[25]

Omadacycline is available in both IV and oral formulations, facilitating discharge from the hospital on the same antibiotic.[16,28,29] Omadacycline is not metabolized by the liver and is not an inhibitor or inducer of major cytochrome P450 enzymes, making clinically relevant drug-drug interactions through hepatic mechanisms unlikely. Omadacycline is not a substrate or inhibitor of most major drug transporters.[26] Patients on an anticoagulant therapy may require downward adjustment of their anticoagulant dosage while taking NUZYRA.[16]

Clinical Safety

The most common adverse reactions (incidence ≥2%) noted in Phase 3 clinical trials were nausea, vomiting, infusion site reactions, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, hypertension, headache, diarrhea, insomnia, and constipation. A mortality imbalance was observed in the CABP clinical trial with eight deaths (2%) occurring in patients treated with omadacycline compared to four deaths (1%) in patients treated with moxifloxacin. All deaths, in both treatment arms, occurred in patients >65 years of age. The causes of death varied and included worsening and/or complications of infection and underlying conditions. The cause of the mortality imbalance has not been established.[16]

No *C. difficile* infections were reported for omadacycline throughout the clinical program completed to date (N=1,947).[19,20,22] *Clostridium difficile* associated diarrhea has been reported with use of nearly all antibacterial agents.[16] However, tetracycline use has been associated with a lower risk of *C. difficile* infections compared to other antibiotics.[30,31]

Dosage and Administration

Omadacycline is a once daily antibiotic. For adult patients with CABP or ABSSSI, omadacycline treatment can be initiated with a 200 mg IV loading dose, prior to transitioning patients to a once daily 300 mg oral or 100 mg IV maintenance dose on day 2. For patients with ABSSSI, treatment may also be initiated with a 450 mg oral loading dose on days 1 and 2.[16]

NUZYRA IV must not be administered with any solution containing multivalent cations through the same IV line. When taking NUZYRA tablets, patients must fast for at least 4 hours and then take with water. No food or drink (except water) for 2 hours after oral dosing.[16]

No dose adjustment is required for patients with renal or hepatic impairment, and no clinically significant differences in the pharmacokinetics of omadacycline were observed based on age, gender, race, weight, renal impairment or end-stage renal disease, and hepatic impairment.[16]

Please see accompanying Full Prescribing Information.

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Lexington, MA
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USA
1 800 828 2088
www.shire.com

02/20/2019

Mr. Roger Citron
osupharm.di@oregonstate.edu

Dear Mr. Citron,

Re: Your medical information request, Ref: 00011889

Your Shire representative Tyrone McBayne forwarded your request.

Please find the enclosed package in response to your request for medical information:

- TAKHZYRO™ (lanadelumab-flyo 150 mg/mL solution for injection)
    - Takhzyro Written Summary
    - A Product Summary Document containing information about the indications and important safety information for TAKHZYRO™ (lanadelumab-flyo 150 mg/mL solution for injection)
    - The Full Prescribing Information for TAKHZYRO™ (lanadelumab-flyo 150 mg/mL solution for injection)

The attached information is provided as a professional courtesy in response to your inquiry. It is intended to provide pertinent data to assist you in forming your own conclusions in order to make healthcare decisions. Shire does not advocate the use of its products outside of approved labeling or the use of investigational drugs not approved by the U.S. Food and Drug Administration. Please refer to the full Prescribing Information.

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Sincerely,

Tangela Battle
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Takhzyro™ (lanadelumab-flyo injection) Written Summary

HEREDITARY ANGIOEDEMA DESCRIPTION AND PATHOGENESIS

Hereditary angioedema (HAE) is a rare and debilitating genetic disease characterized by recurrent and painful swelling (Zuraw 2016; Lumry 2013). Attacks can occur suddenly and manifest throughout the body with laryngeal edema representing the major cause of angioedema-related mortality (Bork 2012). Patients with HAE suffer substantial burden of illness (Banerji 2013; Bygum 2015) and deleterious impacts on health-related quality of life (HRQoL) and psychosocial well-being (Caballero 2014).

Dysregulation of plasma kallikrein activity is the primary pathophysiologic defect responsible for angioedema in patients with HAE (Zuraw 2016; Schneider 2007). Patients with the most common forms of HAE have a quantitative (Type I) or functional (Type II) loss of C1 esterase inhibitor (C1-INH), which normally functions to regulate activity of plasma kallikrein (Lumry 2013; Zuraw 2016). Plasma kallikrein is a proteolytic enzyme that cleaves high-molecular-weight-kinogen (HMWK) to release bradykinin, a potent vasodilator that binds to the surface of endothelial cells, leading to increased vascular permeability and tissue swelling associated with HAE (Suffritti 2014).

HEREDITARY ANGIOEDEMA TREATMENTS

Consensus guidelines recommend a comprehensive HAE management plan that includes prompt access to acute (on-demand) therapy to treat attacks and routine prophylactic therapy to prevent attacks (Farkas 2017; Zuraw 2013; Maurer 2018). Acute treatments currently available in the United States include plasma-derived C1-INH concentrate or recombinant C1-INH, a bradykinin B2R antagonist, and a plasma kallikrein inhibitor (Zuraw 2013). Therapies currently approved in the US for prophylactic treatment of HAE include a human plasma-derived C1-INH concentrate and a synthetic androgen (Zuraw 2013), as well as a plasma kallikrein inhibitor (monoclonal antibody) (Takhzyro PI).

TAKHZYRO PRODUCT DESCRIPTION

Takhzyro™ (lanadelumab-flyo) is a recombinant fully human monoclonal antibody indicated for prophylaxis to prevent attacks of HAE in patients 12 years and older (Takhzyro PI). Lanadelumab binds plasma kallikrein and inhibits its proteolytic activity (Banerji 2017).

Lanadelumab is available as a ready-to-use 300 mg/2 mL (150 mg/mL) solution in a single-dose vial for subcutaneous (SC) administration only (Takhzyro PI). Lanadelumab has a half-life of approximately 2 weeks (Banerji 2017) and a recommended starting dose of 300 mg every 2 weeks (q2wks). A dosing interval of 300 mg every 4 weeks (q4wks) is also effective and may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months.

SUPPORTING CLINICAL EVIDENCE FOR PREVENTION OF HAE ATTACKS

The efficacy and safety of lanadelumab for routine prophylaxis to prevent HAE attacks was assessed in a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 26-week, phase 3 study (HELP Study; Trial 1) (Banerji 2018) and an ongoing open-label extension (Trial 2) (Riedl et al. 2017).

In Trial 1, patients with Type I or II HAE (N=125) were randomized 3:2:2:2 to receive placebo, lanadelumab 150 mg q4wks, lanadelumab 300 mg q4wks or lanadelumab 300 mg q2wks (Banerji 2018). Patients ≥18 years-old were required to discontinue other prophylactic HAE

medications prior to entering the study; however, all patients were allowed to use rescue medications for treatment of breakthrough HAE attacks.

All lanadelumab treatment arms produced clinically meaningful and statistically significant (*P*<0.001) reductions for the primary endpoint of HAE attacks during a 26-week treatment period (Day 0 to 182). For the intent-to-treat (ITT) population, the adjusted least squares mean attack rate was 1.97 attacks/month for the placebo group compared to 0.48, 0.53, and 0.26 attacks/month for the lanadelumab 150 mg q4wks, 300 mg q4wks, and 300 mg q2wks groups, respectively. The reduction in HAE attack rate was consistently higher across the lanadelumab treatment arms compared to placebo regardless prior long term prophylaxis, laryngeal attacks, or attack rate during the 4-week study run-in period (Takhzyro PI). All three lanadelumab treatment regimens also had statistically significant (P<0.001) reductions relative to placebo across all secondary endpoints, including the number of HAE attacks requiring acute treatment from Day 0 to 182 and the number of moderate or severe HAE attacks from Day 0 to 182. Patients treated with lanadelumab were also 2.9 to 7.2 times more likely to achieve a minimal clinically important difference (MCID) of 6 points in total Angioedema Quality of Life (AE-QoL) scores compared with placebo-recipients (*P*≤0.04).

Adverse events that occurred in ≥10% of patients in any lanadelumab treatment group that also occurred at a higher rate than in the placebo group included injection site reactions (52% lanadelumab vs 34% placebo), upper respiratory tract infection (29% lanadelumab vs 32% placebo), headache (21% lanadelumab vs 22% placebo), rash (7% lanadelumab vs 5% placebo), myalgia (5% lanadelumab vs 0% placebo), dizziness (6% lanadelumab vs 0% placebo) and diarrhea (5% lanadelumab vs 5% placebo) (Takhzyro PI). Most TEAEs (98.5%) were mild or moderate in severity. Hypersensitivity reactions have been observed with lanadelumab. Other less common adverse reactions that occurred at a higher incidence in lanadelumab-treated patients compared with placebo included increased aspartate transaminase (2% vs 0%) and increased alanine transaminase (2% vs 0%).

Trial 2 included subjects who completed the double-blind portion of Trial 1 (rollover subjects, n=109) and non-rollover subjects (n=103) (Riedl et al. 2017, Takhzyro PI). Rollover patients, regardless of treatment in Trial 1, received a single dose of Takhzyro 300 mg at study entry and were followed until the first HAE attack. After the first HAE attack, all patients received open-label treatment with Takhzyro 300 mg every 2 weeks. The primary objective of the study is to evaluate the long-term safety of lanadelumab in patients with Type I or II HAE. All efficacy endpoints were exploratory in this uncontrolled, unblinded study. The study will be ongoing until late 2019.

Ann interim analysis was conducted from May 2016 to September 2017 (Shire Internal Data DX-2930-04). At the time of the interim analysis, subjects had received a median of 15 doses of lanadelumab, and all subjects had been exposed to lanadelumab for ≥1 month during the open-label extension study. A total of 75 subjects had ≥1 year of cumulative study experience with Takhzyro (including their experience during Trial 1 and the open-label extension study). Safety data from the ongoing open-label extension study, consisting of 109 rollover patients from Trial 1 and 103 non-rollover HAE patients is consistent with controlled safety data from the Trial 1 (Takhzyro PI).

Study results from this interim analysis reported median (minimum, maximum) and mean (standard deviation [SD]) HAE attack rates during the treatment period of 0 (0, 4.9) and 0.31 (0.62) attacks/month for roll-over patients. For non-rollover patients, the median (minimum,

maximum) and mean (SD) attack rates were 0 (0, 4.1) and 0.28 (0.64) attacks/month, respectively.

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TAKHZYRO™ [package insert]. Lexington, MA Shire US Inc.

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FEBRUARY 2019

Takhzyro Product Summary from the FDA-Approved Prescribing Information

This summary does not include all the information needed to use Takhzyro™ (lanadelumab-flyo) safely and effectively. Shire does not advocate the use of its products outside of the U.S. Food and Drug Administration (FDA)-approved prescribing information.

Please see the enclosed FDA-approved full prescribing information for more information.

INDICATIONS AND USAGE

Takhzyro is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older (Takhzyro PI).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions have been observed. In case of a severe hypersensitivity reaction, discontinue Takhzyro administration and institute appropriate treatment.

REFERENCE

Takhzyro [package insert]. Lexington, MA: Shire US Inc.

Columbia Asthma & Allergy CLINIC

Allergy, Asthma & Immunology Care for Adults & Children

Dr. Stephen Fritz Dr. Sanjeev Jain

Phone: (971)-220-2201 Fax: (888)-569-0563

Oregon Pharmacy & Therapeutics Committee:

I am an allergist and immunologist at Columbia Asthma and Allergy Clinic located in Clackamas, OR, and I am writing to comment on the Medicaid Drug Review of the Hereditary Angioedema (HAE) Class and specifically provide written testimony with respect to Ruconest (recombinant human C1 esterase inhibitor). I am requesting your consideration for RUCONEST® be added as a preferred product for the Oregon State PDL.

RUCONEST® is the first and only recombinant, plasma-free C1-INH product, administered through intravenous injection and has a rapid onset of relief, with a median time of 75 to 90 minutes. RUCONEST® has shown to raise functional C1 levels and activity of C1-INH levels to normal in ≥ 94% of patients.[3]

RUCONEST® provides once-and-done dosing for most patients. In the pivotal randomized controlled clinical trials, 89% of patients received symptom relief after one dose. That percentage increased to 97% of patients in the open-label extension phase.

With respect to dosing allowances, the U.S. Hereditary Angioedema Association Medical Advisory Board issued a statement that recommends that, "all patients with HAE due to C1INH deficiency should have access to at least 2 standard doses of US Food and Drug Administration medicine for on-demand treatment of acute HAE attacks. Because not all patients respond the same to each medication, it is the responsibility of the coordinating expert physician to work with each patient to define the optimal medication(s) for that particular patient."[10] The WAO Guideline; Recommendation also states, "We recommend that all patients have sufficient medication for on-demand treatment of two attacks and carry on-demand medication at all time."11

Per the package insert, "*the recommended dose of RUCONEST is 50 IU per kg with a maximum of 4200 IU to be administered as a slow intravenous injection over approximately 5 minutes. If the attack symptoms persist, an additional (second) dose can be administered at the recommended dose level...not to exceed 4200 IU per dose. No more than two doses (the equivalent of 4 vials) should be administered within a 24-hour period.*" Recognizing that some patients may require a second dose, the appropriate quantity allotted for the treatment of up to 3 acute attacks should be a minimum limit of 12 vials per fill.

As for durability of response, in a recently published study including 127 patients, there were 68 patients with data available 72 hours after receiving a dose of RUCONEST®. The data showed, 93% of those patients receiving RUCONEST® for HAE attacks were free from symptoms for at least 3 days (72 hours). Attack recurrence or onset of new attack symptom within 3 days of initial treatment with RUCONEST® was rare.

As a recombinant, plasma-free option, RUCONEST® has no risk of human pathogen transmission unlike other plasma-derived C1-INH agents. And, more importantly, in the event this category experiences a

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shortage as was the case in 2017, RUCONEST® is available with scalable and reliable supply. As you may be aware, September 15th the FDA posted an advisory stating the "FDA has recently received reports from patients, physicians, and specialty pharmacies that they have been unable to obtain C1-Esterase Inhibitor (Human) Cinryze®. Healthcare providers and patients may wish to consider alternate treatment options". We do believe these shortages have been resolved for the time-being.

Although effectiveness was not previously established in HAE patients with laryngeal attacks in the pivotal trials, recent pooled analysis of laryngeal attacks from six RUCONEST® trials showed efficacy similar to all other attack locations.

Please also consider, RUCONEST® is the only FDA approved product for HAE with Pregnancy Category B classification which, as you know, means Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. By contrast, the other agents in this category have a Category C classification.

With respect to adverse events and safety, RUCONEST® is well-tolerated with a minimal risk of adverse events.[1] Common adverse reactions (≥2%) reported in all clinical trials were headache, nausea, and diarrhea.

Thank you for your consideration of considering that RUCONEST® be added as a preferred product for the Oregon State PDL.

Sincerely,

Stephen Fritz MD

Stephen Fritz, MD

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Phone: (971)-220-2201 Fax: (888)-569-0563

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