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CSL Behring

September 20, 2018

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
2 Liberty Square, 9th Floor
Boston, MA 02109

Dear Dr. Pearson:

CSL Behring appreciates this opportunity to provide ICER with feedback on the draft evidence document for the review of Hereditary Angioedema (HAE).

CSL Behring is a global biotherapeutics leader driven by our promise to save lives. We meet patients' needs using the latest technologies to develop and deliver innovative therapies. The company offers the broadest range of products in the industry for treating coagulation disorders, primary immune deficiencies, hereditary angioedema, inherited respiratory disease, and neurological disorders. CSL Behring's products are also used in cardiac surgery, organ transplantation, burn treatment, prevention of hemolytic disease in newborns. CSL Behring is committed to maintaining the highest product safety standards and to continually improving manufacturing effectiveness. Our global R&D activities focus on the development of innovative new and improved products and manufacturing processes to ensure our continued growth.

HAEGARDA[®] C1 Esterase Inhibitor Subcutaneous (Human) is the only C1-INH subcutaneous injection for the prevention of HAE attacks. In the pivotal trial, HAEGARDA demonstrated a 95% median reduction of HAE attacks compared to placebo and showed a >99% median reduction in number of uses of rescue medication compared to placebo by the subjects in the 60 IU/kg treatment arm (as per the FDA indication). CSL Behring chose to price HAEGARDA responsibly at an acquisition cost of 15% discount (for the average 80kg patient) compared to the lower fixed dose of prophylaxis therapy (Cinryze[®]) and the monoclonal antibody therapy for prophylaxis (Takhzyro[™]). HAEGARDA also may represent significant additional drug cost savings resulting from the >99% median reduction in rescue medication.

CSL Behring has had 35+ years of experience in developing, manufacturing and distributing C1 esterase inhibitor for those living with HAE, targeting HAE at its root cause by replacing missing or dysfunctional C1-INH. The current World Allergy guidelines recommend use of C1-INH therapy as first line for prophylaxis therapy. HAE is a rare hereditary disease that can cause attacks of swelling, and often pain, in specific parts of the body including the stomach, hands, feet, arms, legs, genitals, throat, and face. Depending on the severity of the disease, some people will have many attacks each month, while others will go months without an attack.

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As each HAE patient experiences attacks differently, when developing the study design and inclusion/exclusion criteria for HAEGARDA clinical studies, CSL Behring sought out a range of individuals that experience frequent, and/or severe HAE attacks. The phase III COMPACT trial for CSL-830 (HAEGARDA), was a randomized crossover study design, which differs from a parallel study design. In the COMPACT crossover study, the patients were able to serve as their own control, thereby reducing the influence of confounding covariates. In a non-crossover study (parallel study design) the different treatment (and placebo) groups are at risk for unbalanced covariates. The crossover study design allows for more efficient statistical analysis and requires fewer subjects than non-crossover designs. An example of the importance of the conduct of the clinical trial protocol is found in the patients that were enrolled in the COMPACT phase III trial; the HAE patient's monthly attack rate pre- and post-study in the placebo arm were similar, reflecting more stringency in patient selection evidence.

Within the 16 week crossover study, patients experienced 3.8 attacks while on placebo per month, vs 0.3 attacks while on 60 IU/kg of HAEGARDA. In the Takhyzro trial, patients in the placebo group experienced 1.97 attacks per month, vs .26 attacks with Takhyzro. Thus, it appears that patients in the HAEGARDA trial suffered from a more severe burden of disease. No head-to-head studies between HAEGARDA and Takhyzro have been conducted, so no direct comparisons should be drawn. Additionally, the average severity of attacks was lower in patients who received HAEGARDA than those who received placebo, with 69% of patients on placebo experiencing a severe attack (investigator reported) vs 9% experiencing a severe attack while on HAEGARDA. We believe the study population, and crossover study design demonstrates the strength of the clinical study, yielding favorable outcomes for all patient types.

We appreciate the transparency, rigor, and thoroughness of the model developed by ICER for HAE. We consider the model developed to be valid, and we have several suggestions for notes and clarifications that would provide further background and help with better understanding the results.

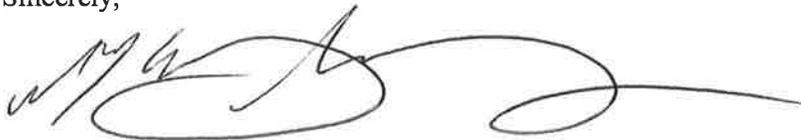
- CSL Behring has conducted and released the analysis of both mean and median results, which demonstrates how outliers impacted the primary results, while still demonstrating what the typical study participant experienced (a 95% median reduction in attacks). It's important to note that when utilizing the mean analysis, outliers can skew the average, therefore misrepresenting the majority of the study population.
- In small patient populations such as HAE, with each patient experiencing varying differences in severity and frequency of attacks, median analysis best represents the majority of the study population.

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- Now that lanadelumab is approved and on the market, we suggest that the placeholder price for lanadelumab be replaced with the actual published WAC price of \$22,070 per dose within the ICER cost effectiveness model.
- Also, in the Potential Budget Impact section on pages 61 and 62, we would suggest that further clarification be given to “Furthermore, lanadelumab compared to a 49%/49%/2% mix of Haegarda/Cinryze/no long-term prophylaxis was cost-saving in all cases except at its estimated placeholder price, mainly due to the higher prices of the prophylactic treatments in the comparator arm.” There are cost and efficacy differences between HAEGARDA and Cinryze, and it may help the report’s audience to understand these differences and how they contribute to the notional cost savings results from the model.

Thank you again for the opportunity to offer our views on this draft evidence document. We look forward to further participation in this process, and would welcome the opportunity to answer any questions you might have for us.

Sincerely,

A handwritten signature in black ink, appearing to read 'Debra Bensen-Kennedy', with a long horizontal flourish extending to the right.

Debra Bensen-Kennedy, MD
Vice President, North America Medical Affairs



September 20, 2018

VIA ELECTRONIC DELIVERY TO: PUBLICCOMMENTS@ICER-REVIEW.ORG

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value: Draft Evidence Report

Dear Dr. Pearson,

Pharming Healthcare, Inc.¹ (“Pharming”) submits this letter in response to the Institute for Clinical and Economic Review’s (ICER) draft evidence report on prophylaxis for patients with hereditary angioedema (HAE). Given the recent request by the FDA for additional clinical data relating to the use of Ruconest (IV formulation) in HAE prophylaxis, Ruconest is no longer being evaluated by the FDA for this indication. Comparators included in ICER’s Evidence Report should be limited to those medications that are FDA-approved for prophylaxis. Pharming therefore requests that ICER remove all information related to Ruconest prophylaxis from consideration to avoid unintended confusion across the health care provider, payer, and patient communities.

RUCONEST® is Not Indicated or Being Reviewed by the FDA for Routine Prophylaxis

Ruconest® (C1 esterase inhibitor [recombinant])² is approved by the United States (U.S.) Food and Drug Administration (FDA) only for the on-demand treatment of acute angioedema attacks in adult and adolescent patients. Unlike the other currently marketed treatments for HAE in ICER’s assessment, Ruconest is not FDA approved, nor undergoing current review, for routine prophylaxis of HAE attacks. The evidence evaluated for Ruconest for routine prophylaxis is limited to two Phase 2 studies (Reshef 2012, Riedl 2017). These trials were neither designed to be Phase 3 pivotal trials, nor intended to be compared with Phase 3 trials such as those included for other comparators in ICER’s evaluation.

Although both of the Ruconest Phase 2 study designs were deemed acceptable for review by the FDA for a supplemental Biologics License Application, Pharming received a Complete Response Letter on September 18th, 2018, in which the FDA requested an additional clinical trial to further evaluate the efficacy and safety of Ruconest for the expanded indication.

Given the recent request by the FDA, it would be misleading and inappropriate to include reference to either comparative clinical or cost effectiveness data related to the use of Ruconest for

¹ Pharming Healthcare is a unit of Pharming Group, N.V., a biotechnology company headquartered in Leiden, The Netherlands. Pharming Healthcare’s offices in the United States are located in Bridgewater, New Jersey.

² Pharming Healthcare, Ruconest Prescribing Information (rev’d Nov. 2017).



prophylaxis in ICER's Evidence Report. Therefore, we request that all reference to Ruconest related to prophylaxis be excluded from ICER's current evaluation.

Minor Revisions and Corrections Requested

Related to the inclusion of Ruconest for On-Demand Treatment, we note the following:

- Table 4.10 (page 42) notes the assumption that 10% of patients receiving Ruconest require an extra dose. In the open label extension phase of Study 1, only 5 of 170 (3%) attacks received a second dose of Ruconest 50 U/kg.³ It should also be noted that in the Berinert clinical trial, 19% of patients (almost 2x ICER's assumed rate) required rescue dosing. Likewise, Firazyr retreatment is set to 15%, whereas ~22% of patients are reported to have had worsening or no prior improvement (Cicardi 2010) and HAE attacks were the most commonly reported spontaneous adverse events (32%) (Malbrán 2014). We request that the percent of attacks requiring extra dose for the on-demand treatments be adjusted to reflect available published data.
- Page 42, Table 4.11. In reference to setting of administration, this table indicates that 33.3% of attacks are treated at home, whereas earlier in the report it is stated that 95% of attacks are treated at home (page 3). As previously reported, purchase patterns for Ruconest also conclude that approximately 95% of volume is shipped direct to the patient, further demonstrating that the site of care is predominantly self-administration in the patient's home. Therefore, we contend the site of care percentages used across the brands for Home Infusion, Physician Office, and Emergency Department sites of care remain overestimated and should be re-assessed.

Pharming appreciates ICER's attention to these considerations and respectfully requests that ICER consider the above suggestions in revising the Evidence Report.

Sincerely,

A handwritten signature in black ink that reads "p.p. Philippe Adams".

Philippe Adams
Vice President, Managed Markets

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³ Ruconest [package insert]. Bridgewater, NJ: Pharming Healthcare Inc.; 2018



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September 20, 2018

Institute for Clinical and Economic Review (ICER)
Two Liberty Square, Ninth Floor
Boston, MA 02109
Submitted electronically via: publiccomments@icer-review.org

RE: Shire's Response to ICER's Draft Evidence Report on Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors

Shire is a dedicated, long-term partner to the Hereditary Angioedema (HAE) community with a decade of experience supporting patients and we appreciate the opportunity to comment on ICER's Draft Evidence Report, "Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value" released on August 23, 2018.

HAE is a rare debilitating genetic disorder that is associated with recurrent attacks of painful swelling events.^{1,2,3} The estimated prevalence of HAE is 1:10,000 to 1:50,000,^{4,5} and it has been estimated that ~6,000 people in the US suffer from HAE.⁵ This translates to approximately 18 cases in a 1 million member plan. HAE is characterized by sudden-onset, recurrent attacks of debilitating pain along with intense, disfiguring swelling that can result in hospitalizations and emergency room visits.⁶ Angioedema attacks can be life-threatening and acute laryngeal edema is the major cause of angioedema-related mortality.^{7,8} When discussing the impact of HAE on their life, one patient noted, "I had excruciating stomach episodes and frightening throat swellings as well. The smallest pressure or slightest muscle pull could set me off. I lived in a world of complete uncertainty."⁹

HAE severity is highly variable and changes over time, requiring an individualized approach to treatment.^{3,5,10} Despite advances made over the past 10 years, patients living with HAE have been seeking new options to help better address their unmet treatment needs. There is significant variability in patient response to therapies, and achieving a meaningful clinical result often requires trial and error by an expert physician.¹¹ Treatment guidelines from the US Hereditary Angioedema Association (HAEA) Medical Advisory Board and the World Allergy Organization (WAO) recommend an individualized care plan crafted by an expert HAE physician in conjunction with the patient.^{5,10}

From our historical work with the HAE community, we have heard first-hand about the need for new treatment options that may be more effective and easier to use. Our commitment to innovation in HAE is focused on addressing these unmet needs and, together with our portfolio of therapy options, we provide specialized services and support offerings that are intended to help meet the individual needs of those living with HAE. Shire fully supports the HAEA position that patient quality of life can only be attained with full access to all FDA licensed HAE therapies.

There are 3 Phase III clinical trials evaluating the efficacy and safety of prophylaxis in people with HAE Type I and II (1 for Cinryze, 1 for Haegarda and 1 for lanadelumab).^{12,13,14} As recognized by ICER in the draft report (pages 6, 14, 16, 17, 29, and 35), these trials have substantial differences in trial design, study populations, and outcome measurements and therefore network meta-analyses

was not conducted and ICER was unable to compare C1 INHs and lanadelumab to each other through direct or indirect quantitative assessment.

The rarity, heterogeneity, and unpredictability of HAE and the substantial differences in clinical trials acknowledged by ICER in their report, which limited the use of rigorous methods, makes it extremely challenging to make fair and balanced comparisons even across incremental cost-effectiveness ratios. This may lead to recommendations that are potentially harmful to HAE patients.

Furthermore, upon reviewing the draft ICER report, we found specific instances of assumptions and inputs that do not accurately account for the way prophylaxis HAE treatments are expected to be used in clinical practice and inaccurate choice of price metrics and methodology to estimate cost of therapies. Below we have provided a summary of our key observations:

1) The model does not reflect lanadelumab's FDA- approved dosing

The analysis assumes that all patients treated with lanadelumab will use 300 mg every 2 weeks for life. The ICER analysis is not representative of the FDA-approved dosing and expected lanadelumab utilization in clinical practice and overestimates the cost of lanadelumab.

2) Choice of price metric in the model is inaccurate and does not result in a fair and balanced comparison across therapies

Without verifying the manufacturer's status as either a single pricer or dual pricer and confirming how they are listing their products on the Federal Supply Schedule (FSS), the most accurate comparison of pricing would be WAC. Furthermore, given the lack of wide-spread discounting in the HAE category, WAC would be a more representative price for payers (vs. FSS/Big 4). At a minimum, Big4 pricing (not FSS) for Shire products is more representative of the purchase price to the vast majority of federal customers.

3) Price calculation methodology used in the analysis for weight-based therapies ignores vial wastage inherent in weight-based dosing and results in underestimation of cost in clinical practice

The current methodology used to calculate the cost of weight-based therapies ignores product wastage that is inherent in weight-based dosing and leads to a potential underestimation of cost in clinical practice.

Detailed key comments:

Addressing the following would likely generate very different results:

1) The model does not reflect lanadelumab's FDA- approved dosing

Per the lanadelumab USPI, the recommended starting dose is 300 mg every 2 weeks. A dosing interval of 300 mg every 4 weeks is also effective and may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months.¹⁵

The lanadelumab dosing modelled in the cost-effectiveness analysis does not reflect the FDA-approved dosing for lanadelumab. The analysis assumes that all patients treated with lanadelumab will take 300 mg every 2 weeks for life.

In the HELP study, the percentage of attack-free patients for the entire 26-week treatment period (Day 0 to Day 182) was 44.4% in the lanadelumab 300 mg every 2 weeks compared to 2.4% of placebo patients.^{14,15} We would expect a subset of the patients who remained attack-free after starting on 300 mg every 2 weeks to be considered for every 4 weeks dosing. This impact of down titration in dosing is not reflected in the model given the model horizon is over the life of the patient.

Therefore the analysis overestimates the expected lanadelumab utilization in clinical practice and the resulting cost of lanadelumab.

2) Choice of price metric in the model is inaccurate and does not result in a fair and balanced comparison across therapies

ICER should not use Federal Supply Schedule (FSS) price as the price metric for subcutaneously administered drugs and self-administered doses of intravenously administered drugs, because the FSS prices included in the model do not consistently represent the same types of discounts among different manufacturers.

The FSS is a government procurement contract where the purchase price to certain federal customers is capped at the Federal Ceiling Price (FCP). Manufacturers have the option to utilize only this single FSS price point (single pricer), or they may establish dual prices (i.e., establish themselves as a “dual pricer”). A dual pricer has a price for the Big4 agencies (VA, DOD, PHS, including the Indian Health Service, and Coast Guard) that does not exceed the FCP and a negotiated, often significantly higher, price for all other government agencies (OGA) eligible to purchase from the FSS.

Shire has chosen to be a Dual Pricer, therefore, when one views the FSS contract pricing for our products on the VA’s website, 2 price points are available:

- FSS Price
- Big 4 Price.

For a dual pricer like Shire, the FSS price shown is the higher OGA price, not the lower Big 4 price. For consistent comparison with a single pricer, the Big 4 Price should be used instead of the FSS price.

FSS and Big 4 prices for Shire HAE products (Cinryze, Kalbitor, and Firazyr)¹⁶

NDC	PKG	CONTRACT	PV	VENDOR	GENERIC NAME	TRADE NAME	FSS PRICE	NC PRICE	BIG 4 PRICE
		NUMBER							
42227-0081-05	500IU	V797P-2306D		Shire US,	C1 INHIBITOR (HUMAN) 500UNITS/VIL INJ,PWDR	CINRYZE C-1 INHIBITOR 500IU/VIL	\$2,751.93	\$0.00	\$2,011.61

NDC	PKG	CONTRACT NUMBER	PV	VENDOR	GENERIC NAME	TRADE NAME	FSS PRICE	NC PRICE	BIG 4 PRICE
47783-0101-01	3X1ML	V797P-2306D		Shire US,	ECALLANTIDE 10MG/ML INJ	KALBITOR 10MG/ML INJ	\$11,173.89	\$0.00	\$8,386.65
NDC	PKG	CONTRACT NUMBER	PV	VENDOR	GENERIC NAME	TRADE NAME	FSS PRICE	NC PRICE	BIG 4 PRICE
54092-0702-02	1	V797P-2306D		Shire US,	ICATIBANT 30MG/3M INJECTION	FIRAZYR 30MG/3M INJECTION	\$7,177.64	\$0.00	\$6,410.52
54092-0702-03	3	V797P-2306D		Shire US,	ICATIBANT 30MG/3M INJECTION	FIRAZYR 30MG/3M INJECTION	\$21,532.91	\$0.00	\$18,464.31

In contrast, CSL Behring, for example, is a Single Pricer. They only have one price, the FSS Price capped at the FCP, for all eligible entities that purchase from their FSS contract.

FSS prices for CSL HAE products (Berinert and Haegarda)¹⁶

NDC	PKG	CONTRACT NUMBER	PV	VENDOR	GENERIC NAME	TRADE NAME	FSS PRICE	NC PRICE	BIG 4 PRICE
63833-0825-02	1	V797D-50358		CSL Behrin	C1 INHIBITOR 500UNTS/VIL INJ,PWDR	BERINERT C1 INHIBITOR 500 IU/VIL	\$1,135.14	\$0.00	\$0.00
NDC	PKG	CONTRACT NUMBER	PV	VENDOR	GENERIC NAME	TRADE NAME	FSS PRICE	NC PRICE	BIG 4 PRICE
63833-0828-02	1	V797D-50358		CSL Behrin	C1 INHIBITOR (HUMAN) 2000UNITS/VIL INJ,SOLN	HAEGARDA 2000UNITS/VIL INJ,SOLN	\$1,393.19	\$0.00	\$0.00
63833-0829-02	1	V797D-50358		CSL Behrin	C1 INHIBITOR (HUMAN) 3000UNITS/VIL INJ,SOLN	HAEGARDA 3000UNITS/VIL INJ,SOLN	\$2,089.78	\$0.00	\$0.00

Please note that the Big 4 price is lower than the FSS Price. This is because that price cannot be higher than the FCP whereas the FSS/OGA Price is a negotiated price not capped at any set price. Since TAKHZYRO (lanadelumab-flyo) is a recently approved product, the Big 4 price has not yet been established. However, the Big 4 price for TAKHZYRO will at a minimum be a 24% discount to WAC given federal mandates on pricing.

The above illustrates why it is inaccurate to use the FSS Price for both a single and dual pricing manufacturer. Without verifying the manufacturer's status as a either a single pricer or dual pricer and confirming how they are listing their products on the FSS, the most accurate comparison of pricing would be WAC. Furthermore, given the lack of wide-spread discounting in the HAE category, Wholesale Acquisition Cost (WAC) would be a more representative price for payers (vs. FSS/Big 4). At a minimum, Big4 pricing (not FSS) for Shire products is more representative of the purchase price to the vast majority of federal customers (e.g., VA, DOD, PHS, including the Indian Health Service, and Coast Guard – the Big 4 Agencies entitled to the price cap at FCP).

3) Price calculation methodology used in the analysis for weight-based therapies ignores vial wastage inherent in weight-based dosing and results in underestimation on cost in clinical practice

Some HAE treatments are dosed by weight and the cost per patient differs by body weight. At a population level the total dose to be given would depend on the distribution of patient weights. By calculating cost based on a single average weight (i.e. for females and males combined), the model ignores the vial wastage inherent in weight-based therapies and underestimates the real cost in clinical practice.

Using Haegarda as an example of a product that is dosed by weight and assuming an average HAE patient weighs 80 kg leads to the calculation of an average WAC per dose of \$4,700 for Haegarda (dosed at 60 IU per kg, an 80 kg patient requires a dose of 4,800 IU → one 2000 IU vial at \$1,880 and one 3000 IU vial at \$2,820).¹⁷ However, this simplistic method of calculating average cost ignores product wastage that is inherent in weight-based dosing and leads to an underestimation of cost. The amount wasted will vary by patient weight. For the 80 kg patient example 200 IU are wasted (~4% of prescribed dose). According to the CDC,¹⁸ an average male weighs around 89 kg and wastage in this case would be 660 IU (~12% of prescribed dose). Cost-effectiveness analyses that assume no drug wastage may not reflect real world practices and actual costs.¹⁹

A more accurate approach to calculating price for weight-based therapies would be to calculate the cost for an average female patient and the cost for an average male patient and then blend the cost based on HAE demographics (proportion of female and male patients). As per ICER review (Page 36), ICER assumes 70% of HAE patients included in the analysis are females and 30% are males.

According to the aforementioned alternate price calculation methodology and using WAC, one Haegarda dose for an average female weighing 76kg would be \$4,700 while an average male patient weighing 89 kg would be \$5,640. Assuming a 70:30 female: male ratio for HAE, the average cost of Haegarda per dose would be \$4,982. This represents a 6% increase over the cost when vial wastage is not taken into consideration.

Conclusion

HAE remains an extremely debilitating life threatening condition and due to the nature of the disease, there is significant variability in patient response to therapies. To achieve meaningful outcomes, patients and physician must be able to develop individualized treatment plans. Without broad access to treatments, we limit the ability of physicians and patients to develop the treatment plan that works best for them, which for many may have a significant impact on their quality of life. Given the limitations associated with the analysis recognized by ICER within the draft report, it is extremely challenging to make fair and balanced comparisons even across incremental cost-effectiveness ratios potentially leading to recommendations that may be harmful to HAE patients.

We appreciate your serious consideration of the issues raised in this letter.

Sincerely,



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September 20, 2018

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President
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One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Evidence Report “Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value”

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with life-threatening conditions and chronic diseases to have access to vital therapies and services. Access is a matter of survival for those patients, and it spans affordability, insurance coverage, and physical access. To support improved access, we are committed to engaging patients, caregivers, physicians, media, health policy experts, payers, providers, and others to foster realistic, patient-centered, solution-oriented discussions for particular conditions and the entire U.S. health care system. That is, our goal is a balanced dialogue that illuminates the truth about health care in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER’s August 23rd Draft Evidence Report, “Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value.”

At the outset, it is important to note that the FDA approved Takhzyro (landelumab) on August 23rd, which coincidentally was the same date as the release of ICER’s draft evidence report.ⁱ With that decision, the exact FDA approved label is now available, which provides real-world information to replace what was only speculative in ICER’s draft evidence report. As we’ve previously stated, “evaluating the clinical and market potential of medicines prior to approval – and by definition prior to the final FDA label of indications and warnings – is extremely difficult.” Therefore, we look forward to reviewing ICER’s updated analyses and conclusions that incorporate this new data, and would hope that ICER would reissue an updated Draft Evidence Report before proceeding to the next stage of its process.

To assist you and your colleagues with that activity, our comments about the August 23rd Draft Evidence Report are below organized into sections concerning: Patient Perspectives and Issues; Humanistic Issues Concerning Budget Analyses (Revisited); Relationships Between Payment Policies and R&D Investments; Analyzing the Benefits of Treatments for Ultra-Rare Conditions; and ICER’s Pricing and Market Assumptions.

Patient Perspectives and Issues

Clearly patients with hereditary angioedema should welcome the significant clinical benefits that the latest preventive option offers them. And having a second preventive medicines that can be

self-administered by subcutaneous injection also provides them more options, which will create market competition to reduce overall costs – and hopefully lower net costs to patients.

We share ICER’s concern about the limited data available for analysis of preventive treatments for hereditary angioedema, with ICER’s analysis only looking at one trial for each treatment option, with the largest trial only including 125 individuals. This is not surprising given the very rare nature of the disease, which means that locating and recruiting patients in particularly onerous and challenging. That is why we were very glad to see that the open label extension (OLE) study for Takhzyro® includes 97% of patients in the HELP trial, indicating that they should be highly representative of the clinical trial population and thus provide reliable and important information about ongoing outcomes and safety. Therefore, because for rare diseases such as hereditary angioedema, incorporating all information into assessments of utility is particularly important, we would suggest incorporating whatever data and information that is available from that OLE study into ICER’s process as soon as possible.

Humanistic Issues Concerning Budget Analyses (Revisited)

ICER’s response to our comments about budget impact issues in the draft evidence report for amyloidosis focused on one aspect, i.e., the concept that health care spending should grow at no more than a certain percentage of the GDP as referenced in “provisions of the Affordable Care Act and the health care cost-control laws in Massachusetts.”ⁱⁱ However, those comments do not address the larger and more important points we made about the historical nature of health care spending, evolutions of technologies and economies, and societal choices and decisions. Therefore, without repeating our comments from that letter here, we would appreciate ICER providing a more in-depth response to those issues and perspectives.

Relationships Between Payment Policies and R&D Investments

In previous lettersⁱⁱⁱ we have mentioned that ICER’s framework modifications for ultra-rare diseases does not consider how payer decisions effect research and development (R&D) priorities and resource allocations. While we were limited by ICER’s space constraints in those letters, because ICER’s recent response was off-point by responding only about how pricing (and presumably reimbursement or net prices) should follow value – a concept we agree with – we feel the need to expand on the very important relationship among payment policies, R&D investments, and patients’ interests, and provide clear and direct insights so that there is no confusion for ICER about those important relationships.

As you know, there is a direct and causal relationship between investments in R&D and the availability of future new medicines, diagnostics, and other treatment innovations, which are all important to patients. What is equally important is that there is a linked, direct and causal relationship between what and how payers reimburse for different diagnostic and therapeutic options for specific diseases and conditions, and the investment decisions in those disease areas. Thus, while patients are concerned about their ability to afford health care services and products, for those that involve innovations (i.e., are not commodities), they also want substantial R&D, which requires adequate or robust payment policies for existing diagnostic and treatment options in those same disease areas in order to encourage more R&D.

The fundamental dynamics of those relationships are that payment practices (and amounts) send

signals to investors (both companies for internal allocation decisions and outside investors) as to what are the most financially attractive opportunities for their resources. There is extensive literature about how reimbursement and payment practices have driven changes in care delivery – such as hospitals buying or building certain types of care delivery, including, cardiology and oncology.^{iv} And there have also been studies about how reimbursement affects biopharmaceutical and medtech investments.^v

Thus, if payers communicate through minimal reimbursement amounts or barriers to payment for a particular condition or disease, then clinicians and institutional providers won't commit resources to providing or expanding services for those illnesses. This was the case with mental health and substance abuse treatment until relatively recently. And conversely, if payers communicate via their payment practices that they will pay a premium for certain types of care, then clinicians and providers will seek to provide (and invest in expanding) those services, e.g., hospital outpatient oncology services. A similar process occurs with biopharmaceutical and medtech companies and their outside investors. That is, if there is a market opportunity created by payers' premium reimbursements for diagnosing or treating a clinical condition, then investors will follow. And conversely, if payers squeeze or block reimbursements for particular clinical conditions or sites of care, then companies and investors will deprioritize or avoid those areas.

What this means for patients concerned about specific disease areas is that they want investments in that disease area to be very attractive – which clearly requires prioritized payment processes and relatively higher amounts. For example, if someone learns that they (or their child) have a genetic marker that gives them a high chance of developing a certain condition (such as hereditary angioedema, or amyloidosis – which has a more variable age of onset), then they want companies to put lots of scientists and research time into finding better treatments and hopefully a cure. But for a company to do this, they not only need new scientific insights, but they will also examine how payers are reimbursing for current treatment options. They may ask, “Does the current market landscape indicate that payers will pay a premium price for access to treating that condition, including access to doctors, hospitals, other clinicians, and diagnostics?” Or does it communicate that payers will erect high barriers and refuse to pay for new treatments above commodity prices for existing treatments in order to control their spending – regardless of the benefits the new treatment has for patients?

Those relationships are heightened in the area of rare diseases because the costs of innovative therapies are inherently higher than average. If payors or regulators are going to adopt broad upper limits on any and all new treatments, then that will dramatically diminish investment into new diagnostics and treatments for diseases with limited patient populations. The long-term consequences of low payment amounts or barriers is that there will be fewer treatment options, and higher morbidity and mortality for those individuals.

We hope our insights on this matter provide some clarity to what we have seen as a blind spot for ICER about the real-world market dynamics and the relationships between payer actions and R&D investments.

Analyzing the Benefits of Treatments for Ultra-Rare Conditions

Extending the discussion above, we hope that ICER will incorporate this knowledge into its processes for ultra-rare conditions, because with this understanding ICER should now realize that asking about R&D and manufacturing spending is non-sensical. That is, while ICER correctly notes that the price of medicines should be connected to the value it provides to patients (and society), it is logically inconsistent to then request information about R&D and manufacturing costs because clearly those costs and the actual value a new medicine provides are not causally connected. For example, if aliens from Alpha Centuri landed and told Elon Musk how to make cars that ran on water (using anti-gravity or cold fusion technology), the price he charged for those extraordinary cars wouldn't reflect the R&D costs – which would have been essentially zero. Similarly, if those same sentient beings provided a biopharma company with a cure for hereditary angioedema (or Alzheimer's) that was relatively easy and inexpensive to produce, the value of such a cure would be completely disconnected from the R&D or manufacturing costs. Therefore, requesting R&D or manufacturing costs for a single medicine is a quixotic red herring apparently intended to connect ICER's analytical process to unrelated metrics.

ICER's Pricing and Market Assumptions

As we noted above, since the release of the draft evidence report, the FDA has approved lanadelumab. This again is an example of how ICER's process of assumption filled analyses incorrectly models the real world. Similarly, ICER's assumptions about pricing and discounts are highly dubious. Specifically, in the August 23rd draft evidence report's budget impact calculations, ICER assumes a 7.4% discount from its placeholder price.^{vi} We would like to understand how ICER decided to use this 7.4% discount amount since in previous reports ICER has used other discount levels, e.g., 29%^{vii}

We are very concerned about using this 7.4% discounted price for several reasons. First, comparing a discounted price to the Federal Supply Schedule (FSS) prices for other approved medicines is an unbalanced comparison since the ceiling for FSS prices under Federal law is required to be at least a 24% discount off the non-Federal Average Manufacturer prices, with the additional requirements that FSS prices cannot rise faster than inflation and they cannot be greater than the prices paid by private payers who buys the medicines on terms similar to those of the Veterans Administration. And as a recent analysis showed, the actual discount for FSS prices compared to wholesale prices was often on the order of 40-70%.^{viii} And second, examining ICER's analyses as reported in Table 4.13 on page 45 of the draft evidence report, a 21% discount from the placeholder price would result in an effective "break-even" price for total U.S. health system costs. And further, a price reduction (from the placeholder price) of 29% would result in a net price equivalent to Haegarda. We make these points in order to help ICER clarify and refine its methodology – or at least improve its transparency about its assumptions and calculations.

Additional Note

- In this report health care is sometime one word ("healthcare"), and sometimes it is two words, even though in your recent response to comments you agreed that it is two words.

Conclusions & Recommendations

Ralph Waldo Emerson – an eminent thinker from ICER’s home in the Boston area – is famous for his quote that “A foolish consistency is the hobgoblin of little minds, adored by little statesmen and philosophers and divines. With consistency a great soul has simply nothing to do. He may as well concern himself with his shadow on the wall.”^{ix}

We remain concerned that ICER is continuing to retain its adherence to certain analytical concepts that are inconsistent with the real world – such as a fixation on R&D or manufacturing costs. This warped perspective could lead patients, policy makers, and others (including payers and clinicians) to focus on the “shadow on the wall” that is not only ethereal, but distorted by the ICER’s misguided assumptions, lack of transparency about those assumptions, and an overly simplified construct of the U.S. health care financing, delivery, and innovation systems.

Patients Rising Now believes that ICER’s draft report on some treatment options hereditary angioedema inadequately reflects patients’ perspectives, and its misunderstanding of how investment decisions for biomedical R&D are made, leading to warped conclusions. That is, outputs from models are only as valid as both the assumptions used to build the model and the data fed into those models. In both those areas, ICER continues to have serious deficiencies, and thus it is producing flawed outputs. We hope that ICER will expand its analytical realm to include more – and more varied – real-world expert viewpoints so that your reports are more properly useful for improving the operations of different parts of the complex and pluralistic U.S. health care systems, rather trying to opine about an imaginary homogenous system.

Sincerely,



Terry Wilcox

Co-Founder & Executive Director, Patients Rising Now

ⁱ <https://www.fda.gov/Drugs/DrugSafety/ucm618261.htm>

ⁱⁱ “Response to Public Comments on the Draft Evidence Report,” ICER, August 29, 2018

ⁱⁱⁱ Patient’s Rising Now Comment Letters about ICER Draft Evidence Reports, “Modulator Treatments for Cystic Fibrosis: Effectiveness and Value,” April 12, 2018 & “Draft Evidence Report “Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value,” August 17, 2018

^{iv} “Specialty-Service Lines: Salvos In The New Medical Arms Race,” Berenson et al., Health Affairs, Sept./Oct. 2006; “Expansion of Invasive Cardiac Services in the United States,” Horwitz, et al., Circulation, July 19, 2013; “Service-line strategies for US hospitals,” The McKinsey Quarterly, July 2008; “Hospital ownership of physician practices on the rise,” Medical Economics, Sept. 24, 2016; “The Oncology Drug Marketplace: Trends in Discounting and Site of Care,” Berkeley Research Group, December 2017.

^v “The Impact of Reimbursement Policies and Practices on Healthcare Technology Innovation” HHS Assistant Secretary for Planning and Evaluation, February, 2016, and “Value and Coverage: How Reimbursement Decisions Impact Innovations Needed to Improve Health”, FasterCures, January 2014

^{vi} “Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors,” ICER, August 23, 2018, p. 58

^{vii} “Antiandrogen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer,” ICER, July 12, 2018, p. 37

^{viii} “Estimating Drug Costs: How do Manufacturer Net Prices Compare with Other Common US Price References?” Mattingly, et al., Pharmacoeconomics, p. 1093-99, May 12, 2018; “Prices for Brand-Name Drugs Under Selected Federal Programs,” Congressional Budget Office, June 2005

^{ix} <https://www.goodreads.com/quotes/353571-a-foolish-consistency-is-the-hobgoblin-of-little-minds-adored>