INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors

Response to Public Comments on Draft Evidence Report

October 11, 2018

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Manufacturers		
CSL Behring		
1.	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. (1) 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.	We have included the median results in the clinical effectiveness section of the report. However, mean values are the recommended measure for use in cost-effectiveness analyses as they represent the expected outcomes for the entire population.
2.	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.	Please see the response above.
3.	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.	We have updated the model to reflect the WAC and FSS prices of lanadelumab.
4.	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.	We have revised this sentence to note that the higher cost of the comparator mix is mainly due to the higher costs associated with prophylactic treatment with Cinryze.
Pharming		
1.	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	Given that the FDA has declined to approve Ruconest's expanded indication until further clinical evidence can be provided, we have elected to remove it from the clinical and economic analyses in the revised Evidence Report.

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	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 prophylaxis in ICER's Evidence Report. Therefore, we request that all reference to Ruconest related to prophylaxis be excluded from ICER's current evaluation.	
2.	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. 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.	We have updated these parameters in the model using the most appropriate data from peer reviewed sources. Estimates of the proportion of attacks requiring an extra dose for each drug were 1.9% for Berinert (Zanichelli et al, 2015), 12% for Kalbitor (Li et al, 2013), 12.7% for Firazyr (Zanichelli et al, 2015), and 10.1% for Ruconest (Riedl, 2013).
3.	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.	To clarify our assumptions, we distinguish between prophylaxis and on-demand treatment: 1. 95.2% of **intravenous prophylactic treatment** (i.e., Cinryze) is self-administered. 2. The distribution of setting of administration of **on-demand treatment** of mild and moderate attacks is 64.9% self at home, 13.8% home nurse, and 21.3% outpatient. 3. In Table 4.11, which we have removed from the revised report, we did not intend to imply that 33% of attacks are treated at home. Rather, for all mild and moderate attacks that are treated at home by patients themselves, we assumed an equal distribution across all possible on-demand treatments. That is, 33.3% of attacks would be treated with Berinert, 33.3% of attacks would be treated with Firazyr, and 33.3% of attacks would be treated with Ruconest.
Shire		
1.	(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	Our analysis now includes a scenario analysis modeling the reduction of dosing frequency to every for weeks in patients who were attack-free

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	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. 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. The lanadelumab dosing modelled in the cost-effectiveness analysis does not reflect the FDA-approved dosing for lanadelumab. 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. 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.	on lanadelumab for six months. We are including this as a scenario (rather than the base case) analysis because: 1. The label states that switching to every four weeks "may be considered" in patients who are well controlled (i.e., attack free) after six months. 2. The open-label study of lanadelumab is dosing patients every two weeks. 3. There are no data on the proportion of patients that would switch. 4. There are no data on the effect of switching on the attack rate or ability to sustain "attack-free" status.
5.	(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: (1) FSS Price, and (2) 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.	To ensure consistency, the revised report now uses Big 4 prices for "dual pricers," and FSS prices for "single pricers."

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6.	(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. 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 à one 2000 IU vial at $1,880 and one 3000 IU vial at $2,820). 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, 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. 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.	We have adapted this approach to price calculations for all drugs which are dosed according to weight. The approach also accounts for wastage. For instance, for Haegarda, we have added the following statement to the report that reflects our approach: "For Haegarda which is dosed according to weight, we used gender-specific weight distributions (i.e., mean and standard deviation) to calculate the average number of 2,000 IU and 3,000 IU vials, accounting for wastage and selecting the vial combination with minimum cost from all possible vial combinations."
Patient Advocacy Groups		
Terry Wilcox, Co-Founder & Executive Director, Patients Rising Now		
1.	...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	Thank you for your comment. There are currently no data available on the open-label extension for the HELP trial, as the trial is still ongoing.

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	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.	
2.	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." 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.	Earlier comments pointed out that the level of health care spending has changed over time, that technologies and the economy are dynamic and evolve over time, and that societal preferences may change and influence health care spending levels over time. All of this is true, which is part of the reason that ICER revisits the rationale for and updates calculation of the budget impact threshold on a periodic basis.
3.	In previous letters 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.	We agree that there are relationships between levels of pricing and reimbursement and levels of investments in R&D. We also believe that there should be a relationship between all of these and the value provided by innovative treatments. Our framework adaptation for ultra-rare diseases recognizes that payers may wish to consider other aspects of value when evaluating treatments for such conditions, including higher willingness-to-pay thresholds, societal impacts, and other benefits and contextual considerations, that may lead to coverage and funding decisions at higher prices.
4.	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	We feel the commenter is misunderstanding the point of this request. We have heard at times that manufacturers of drugs for ultra-rare conditions feel that R&D costs are important elements in justifying the list prices of their drugs, and we feel that it is important to highlight these instances. Also note that R&D costs have not influenced clinical or economic analyses in our report; they are included as contextual information.

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	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.	
5.	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. 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%. 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%. 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.	As lanadelumab has now received FDA approval, we have updated our analyses to use the published WAC and FSS prices for lanadelumab. The FSS price reflects a 25% discount from WAC.
6.	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.	Thank you for pointing out this oversight. We note that this does not affect the conclusions of our report.
7.	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	As mentioned above, ICER has no focus on R&D or manufacturing costs other than to allow manufacturers of treatments for ultra-rare conditions the option of providing such information if they feel it provides an alternative justification to value-based pricing. Given the

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	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.	current structure of the US health care market, there are few constraints on those who would set prices without regard to benefits to patients and society.