

## Summary

### WHAT IS HEREDITARY TRANSTHYRETIN AMYLOIDOSIS (HATTR)?

hATTR is a rare, progressive, and fatal multi-system illness caused by misfolding deposits of transthyretin (TTR), a protein produced by the liver. Over time, these deposits cause significant neurologic problems, functional limitations, and disability. Some patients also develop cardiac complications, which can increase the risk of early death. The age of onset of symptoms, the types of problems patients experience, and the rate of progression vary significantly.

### TREATMENT OPTIONS

Treatment options include liver transplant and diflunisal, an off-label non-steroidal anti-inflammatory drug (NSAID) that stabilizes the TTR protein and reduces abnormal deposits. Use of these treatments is typically limited to relatively healthy, younger patients with hATTR, and neither treatment reverses the damage already caused by TTR deposits.

ICER's report reviewed two new treatments for hATTR, both of which have the potential to reverse the damage caused by protein deposits:

- Inotersen (investigational, Akcea Therapeutics), given by injection once every week
- Patisiran (Onpattro™, Alnylam Pharmaceuticals), given by IV infusion once every three weeks

Patisiran was approved in August 2018 for treatment of neurologic damage related to hATTR, and an approval decision on inotersen for a similar indication is expected in October 2018.

Because the size of the patient populations eligible for treatment with these drugs is fewer than 10,000 individuals, ICER applied its framework for treatments of ultra-rare disorders.

### KEY REPORT FINDINGS

ICER's report found that both inotersen and patisiran provide a substantial net health benefit when compared to best supportive care alone, but current pricing far exceeds commonly cited thresholds for cost-effectiveness. The report was the subject of a public meeting of the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC).

### KEY POLICY RECOMMENDATIONS

- Given that newly approved treatments for hATTR have new mechanisms of action, lack long-term safety and efficacy data, and are very expensive, it is reasonable for insurers and other payers to develop prior authorization criteria to ensure prudent use of these treatments.
- Manufacturers should bring the price for innovative treatments for hATTR down to a level that aligns fairly with the added benefits for patients.
- Future research should address the durability of improvements in neurological function, longer-term safety, and cardiac outcomes provided by treatments for hATTR.

## Clinical Analyses: ICER Evidence Ratings

### How strong is the evidence that inotersen and patisiran improve outcomes in patients with hATTR?



**Inotersen:** Evidence provided moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit.



**Patisiran:** Evidence provided moderate certainty of a substantial net health benefit with high certainty of at least a small net health benefit.

### KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

ICER's report reviewed three clinical benefits:

- **Neurologic impairment**, measured by the modified Neuropathy Impairment Score +7 (mNIS+7): The mNIS+7 is a measure of motor, sensory, and autonomic neuropathy (nerve damage). The trials for patisiran and inotersen used slightly different versions of this measure, both of which were developed specifically to measure hATTR polyneuropathy.
- Neuropathy-related **quality of life** measured by the Norfolk-QOL-DN questionnaire.
- **Walking ability** measured by FAP stage and PND score: The familial amyloid polyneuropathy (FAP) stage categorizes a patient's ability to walk into three stages: walking unassisted with mild neuropathy, walking with assistance and moderate neuropathy, or being wheelchair- or bed-bound with severe neuropathy. The polyneuropathy disability (PND) score categorizes patients similarly, but with additional attention to impaired walking with or without use of walking aids.

## Clinical Analyses: ICER Evidence Ratings (continued)

### INOTERSEN COMPARED TO PLACEBO

Inotersen slowed the progression of neurologic impairment and stabilized neuropathy-related quality of life compared to placebo.



**Neurologic Impairment**  
*Modest improvement*



**Quality of Life**  
*Modest improvement*



**Walking Ability**  
*No differences*

### PATISIRAN COMPARED TO PLACEBO

Patisiran improved neurologic impairment and neuropathy-related quality of life and improved or stabilized most patients' ability to walk compared to placebo.



**Neurologic Impairment**  
*Large improvement*



**Quality of Life**  
*Large improvement*



**Walking Ability**  
*Small improvement*

## Clinical Analyses: ICER Evidence Ratings (continued)

### HARMS

In the Phase III trial of inotersen, thrombocytopenia (low blood platelet count) and glomerulonephritis (a type of kidney disease) were safety concerns, but these were thought to be manageable with enhanced monitoring. One of five deaths in the inotersen arm was considered possibly drug-related.

The most common side effects in the Phase III trial of patisiran were peripheral edema and infusion-related reactions. Four serious adverse reactions of atrioventricular (AV) heart block occurred in patisiran-treated patients (2.7%), including three cases of complete AV block. No serious adverse reactions of AV block were reported in placebo-treated patients. Otherwise, rates of side effects and death did not differ between patisiran and placebo.

Thirty percent of patients in the inotersen trial developed anti-drug antibodies, while far fewer developed such antibodies in the patisiran trial. Both drugs require longer-term data to determine whether these antibodies impact drug safety and/or efficacy.

### SOURCES OF UNCERTAINTY

**Evidence limitations:** Historically, hATTR has been diagnosed as two separate conditions affecting two separate organ systems. Most literature – including the patisiran and inotersen trials – detail the polyneuropathy and cardiomyopathy manifestations in isolation, and it remains uncertain exactly how these two pathologies of a multi-system disease interact.

**Key outcome measures:** Neither the mNIS+7 nor the Norfolk-QOL-DN have validated thresholds defining a minimum clinically important difference, making it unclear what magnitude of change is important and perceptible to patients.

**Generalizability of trial results:** Cardiac benefits of both drugs are unclear, as each trial focused primarily on enrolling patients with neurologic symptoms. It is also unclear whether trial data are generalizable to patient populations who have received liver transplants, have moderate to severe heart failure, or are using combination gene silencing and TTR stabilizer treatment.

**Long-term effects:** Data on the long-term safety of both new drugs is still emerging, particularly regarding enhanced monitoring for platelets and renal function for inotersen patients, and for long-term dexamethasone use for patisiran patients.

## Economic Analyses

### LONG-TERM COST-EFFECTIVENESS AT LIST PRICE

**Do these treatments meet established thresholds for long-term cost-effectiveness?**

At the net price of \$345,000 for patisiran, and the assumed net price of \$345,000 for inotersen, **both therapies exceed commonly cited thresholds for cost-effectiveness** of \$50,000–\$150,000 per quality-adjusted life year gained when compared to best supportive care.

Inotersen	Patisiran
\$1.7 million per QALY gained*	\$835,000 per QALY gained

*\*As a price was not available for inotersen at the time of this publication, patisiran’s net price was used as a placeholder price for inotersen.*

### VALUE-BASED PRICE BENCHMARKS

**What is a fair price for inotersen and patisiran based on their value to patients and the health care system?**

	Annual List Price	Net Price	Annual Price to Achieve \$100,000–\$150,000 per QALY Thresholds	Discount from WAC Required to Reach Threshold Prices	Net price within range?
<b>Inotersen</b>	\$450,000*	\$345,000*	\$15,300–\$25,400	94% to 97%	NO
<b>Patisiran</b>	\$450,000	\$345,000	\$24,700–\$46,500	90% to 95%	NO

*\*As a price was not available for inotersen at the time of this publication, patisiran’s price was used as a placeholder price for inotersen.*

### POTENTIAL SHORT-TERM BUDGET IMPACT

**How many patients can be treated with inotersen or patisiran before crossing ICER’s \$991 million budget impact threshold?**

For each of the drugs, the annual potential budgetary impact of treating the entire eligible population over five years **did not exceed** the \$991 million ICER budget impact threshold at the list price or net price, largely due to the **relatively small number of patients eligible for treatment**.

However, the potential budget impact reached 59% of the threshold with inotersen treatment using the estimated placeholder list price of \$450,000 per year, and 80% of the threshold with patisiran treatment when using the list price of \$450,000 per year, suggesting an **outsized impact relative to the number of individuals affected**.

## Voting Results

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The Midwest CEPAC deliberated on key questions raised by ICER's report at a public meeting on September 13, 2018. The results of the votes are presented below. More detail on the voting results is provided in the [full report](#).

### CLINICAL EVIDENCE

The panel found evidence sufficient to show a net health benefit of both inotersen and patisiran, compared to best supportive care alone. However, evidence was insufficient to distinguish between the two treatments.

### OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

Before voting on value, panel members weighed the therapies' other benefits and contextual considerations. The panel unanimously recognized that the novel mechanism of action was an important other benefit for treating individuals with such a high lifetime burden of illness. A majority also recognized that the new treatments may reduce family and caregiver burden and may improve a patient's ability to return to work. These panelists emphasized that the burden that a hereditary disease places on families cannot be understated, and that these new treatments may also have a positive psychological effect on multiple generations of a family.

### LONG-TERM VALUE FOR MONEY

The panel voted unanimously that both inotersen and patisiran represent a low long-term value for money. The votes were influenced heavily by the \$450,000 annual list price of patisiran, and the assumption that inotersen would be priced similarly.

# Policy Recommendations

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The Midwest CEPAC Panel participated in a moderated policy discussion that included physicians, patient advocates, manufacturer representatives, and payer representatives. None of the resulting policy statements should be taken as a consensus view held by all participants. For a more detailed discussion, please see the [full report](#).

### FOR PAYERS

- Given that newly approved treatments for hATTR have new mechanisms of action, lack long-term safety and efficacy data, and are very expensive, it is reasonable for insurers and other payers to develop prior authorization criteria to ensure prudent use of these treatments.
- Payers should negotiate discounts to seek the best value for patients and the health system by bringing the net price of these treatments closer to traditional cost-effectiveness ranges. Savings achieved through these negotiations should be shared with patients to reduce the financial toxicity of long-term treatment.
- Payers and other policymakers seeking to judge the value of patisiran and inotersen should recognize the heightened responsibility to consider the treatments' broader benefits to patients, caregivers, and society while simultaneously working to maintain affordability of health insurance for all patients now and in the future.
- Given that clinicians cannot predict which treatment will be most effective for any individual patient, payers may be able to achieve lower prices for the health system and for patients by applying a step therapy policy favoring the less expensive treatment.

### FOR MANUFACTURERS

- Manufacturers should bring the price for innovative treatments for hATTR down to a level that aligns fairly with the added benefits for patients.
- The high level of uncertainty regarding the long-term safety and effectiveness of patisiran and inotersen suggests that a reasonable price should be lower at the launch of these drugs and only rise to full value-based levels after more robust demonstration of their overall benefits for patients and families.

### FOR PATIENT ADVOCACY ORGANIZATIONS

- Patient organizations that have a leading role in funding, organizing, and promoting innovative research on new treatments should demand commitments from manufacturers for reasonable value-based pricing of the products patients helped bring to the market.
- Patient organizations should also work with payers to ensure that they understand how diverse the patient population with hATTR is and how important access to effective treatments will be for individuals and their families.

## Policy Recommendations (continued)

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### FOR PROVIDERS

- Specialists involved in the care of hATTR should rapidly convene, in partnership with patients, manufacturers, and payers, to develop evidence-based guidelines for appropriate use of new agents.
- Professional societies should highlight the patient impact of failed pricing and insurance policies, and demand to be part of a public process to guide policies that balance the goals of affordability and of ample incentives for investments in future innovation.

### FOR FUTURE RESEARCH

- Future research should address the durability of improvements in neurological function, longer-term safety, and cardiac outcomes provided by treatments for hATTR.
- Future research is needed to validate modified outcome measures used as the basis for regulatory approval for treatments of hATTR.

## About ICER

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The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public

hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit ICER's website ([www.icer-review.org](http://www.icer-review.org)).