

# VALUE-BASED AGREEMENTS IN RARE DISEASE: FOCUS ON HEREDITARY AMYLOID TRANSTHYRETIN AMYLOIDOSIS

## A STAKEHOLDER INTERCHANGE REPORT

The *American Journal of Managed Care*<sup>®</sup> hosted a scientific interchange titled “Value-Based Agreements in Rare Disease” on September 30, 2020. The event included a select group of payers and health economists and was comoderated by **Jim Kenney**, president of JTKENNEY, LLC, in Waltham, Massachusetts, a managed care consulting practice, and **Sami Khella, MD**, professor of neurology and chief of the Department of Neurology of the University of Pennsylvania School of Medicine in Philadelphia. The 10 participants discussed unique features of value-based agreements (VBAs) in rare diseases, the challenges in diagnosing hereditary amyloid transthyretin (hATTR) amyloidosis, clinical efficacy and positioning of recently approved agents, and considerations regarding implementation of VBAs in hATTR amyloidosis.

### VBAs IN RARE DISEASE

The VBAs represent an innovative payment model in which biopharmaceutical manufacturers and health care payers agree to link coverage and reimbursement to the effectiveness and utilization frequency of a drug.<sup>1</sup> VBAs can help drug manufacturers differentiate their product from that of their competitors through agreed-upon outcomes, which helps payers make formulary decisions, and payers can use VBAs to reduce uncertainty regarding the clinical value, effectiveness, performance, and financial impact of a new product.<sup>1</sup> General challenges to implementation include the need for payer, provider, and manufacturer agreed-upon infrastructure to oversee and capture outcomes; reluctance among manufacturers to accept financial consequences if they are unable to control how the patient is compliantly managed and the drug is prescribed; and the difficulty in reaching an agreement on meaningful and measurable outcomes that can be achieved within a reasonable time frame.<sup>1</sup>

Development of VBAs occurs in 4 phases that consider desirability, risks and uncertainties, and the goal of enabling better patient access. The first phase involves ideation between the health plan and/or pharmacy benefit manager and the pharmaceutical manufacturer, desirability and feasibility of a VBA, and identification of potential partners. Phase 2 involves early, informal discussions between 2 parties to discuss capabilities to manage, possible VBA outcomes and measures, negotiations, and confirmation of mutual interest. Phase 3 is a formal negotiation, in which the 2 parties discuss and align with terms and conditions, process to capture and measure outcomes, and the establishment of a written contract. The fourth phase begins when

the parties sign a VBA and begin to execute the terms and activities specified in the contract.<sup>2</sup> According to Kenney, VBAs can be used for any disease type (chronic, acute, or rare/orphan) that has identifiable and measurable outcomes (or a proxy), which can be population based or focused on the individual.

Kenney shared that most VBAs are upside risk agreements and have specific compliance and patient adherence requirements. “For the most part, the manufacturer wants to ensure that the patient was on the drug [and] they were [adherent to] therapy,” said Kenney. “You can use either medication possession ratio or proportion of days covered, as a way to determine whether or not a patient was [adherent] on a medication that’s taken on a scheduled basis.”

Kenney added that the overall goal for health plans is to achieve the best possible patient outcomes, with the appropriate use of products based on clinical data and reduction of financial risk (which can be product specific or occur more broadly through reduced hospitalizations or long-term complications).

In addition, he said that health plans are aiming to reduce uncertainties and risk associated with the patient population and the therapy, increase rebates and savings, and maximize value from the money they invest in these therapies. However, he noted that measurement of outcomes remains an ongoing challenge for the parties involved in negotiating a VBA. The timeline and metrics are carefully chosen, with most contracts having at least a 2-year timeline to facilitate accrual of patients and outcomes, and ensure the risk is balanced for all parties. According to Kenney, ongoing challenges in negotiating VBAs also include methods of data collection through pharmacy or medical records and the availability of these data from electronic medical or health records, options for validation, third-party participation, and assurance of Health Insurance Portability and Accountability Act requirements.

Kenney noted that success in implementation of a VBA can be hindered by transaction and data-capture administrative costs, particularly if there is a small number of patients with the condition in the health plan or the value of the outcomes agreement is low. In addition, limitations in information technology (IT) and scarcity of IT resources may interfere with the ability to extract the data needed to analyze the potential of a new VBA. “It’s helpful to develop those systems so that you can get data when you need it on your own schedule, and you’re not relying on an ad hoc request coming in, out of the IT group, to get at that data,” said Kenney.

(CONTINUED ON PAGE 7)



## INDICATIONS AND USAGE

TEGSEDI® is a transthyretin-directed antisense oligonucleotide indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

## IMPORTANT SAFETY INFORMATION

### **WARNING: THROMBOCYTOPENIA AND GLOMERULONEPHRITIS**

*See additional safety information, including full Boxed Warning, in accompanying Brief Summary.*

#### Thrombocytopenia

- TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, which can be life-threatening
- Testing prior to treatment and monitoring during treatment is required

#### Glomerulonephritis

- TEGSEDI can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure
- Testing prior to treatment and monitoring during treatment is required

TEGSEDI is available only through a restricted distribution program called the TEGSEDI Risk Evaluation and Mitigation Strategy (REMS) Program.

Please see brief summary of full Prescribing Information, including boxed WARNING regarding the risk of thrombocytopenia and glomerulonephritis, on the following pages.

In adults with the polyneuropathy of hereditary ATTR amyloidosis,

# TARGET THE SOURCE WITH TEGSEDI®. CONNECT PATIENTS TO WHAT'S IMPORTANT.

TEGSEDI binds to *TTR* mRNA, silencing the gene and powerfully inhibiting TTR production.

AKCEA® CONNECT is here to provide support and reliable resources patients can trust.



## IMPORTANT SAFETY INFORMATION

### CONTRAINDICATIONS

TEGSEDI is contraindicated in patients with

- Platelet count below  $100 \times 10^9/L$
- History of acute glomerulonephritis caused by TEGSEDI
- History of a hypersensitivity reaction to TEGSEDI

### WARNINGS AND PRECAUTIONS

- *Stroke and Cervicocephalic Arterial Dissection:* TEGSEDI may cause stroke and cervicocephalic arterial dissection.
- *Inflammatory and Immune Effects:* Serious neurologic adverse reactions consistent with inflammatory and immune effects occurred.
- *Liver Injury:* Monitor alanine aminotransferase, aspartate aminotransferase, and total bilirubin every 4 months during treatment and in case of symptoms of hepatic dysfunction.
- *Liver Transplant Rejection:* In patients with a history of liver transplant, monitor ALT, AST, and total bilirubin monthly. Discontinue TEGSEDI in patients who develop signs of liver transplant rejection.
- *Hypersensitivity Reactions:* If these occur, discontinue and initiate appropriate therapy.
- *Uninterpretable Platelet Counts:* Reaction between Antiplatelet Antibodies and ethylenediaminetetra-acetic acid: Platelet clumping can cause uninterpretable platelet measurement; repeat test if this is suspected.

Hold TEGSEDI dosing until an acceptable platelet count is confirmed with an interpretable blood sample.

- *Reduced Serum Vitamin A Levels and Recommended Supplementation:* Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur.

### ADVERSE REACTIONS

The most common adverse reactions (those that occurred in at least 20% of TEGSEDI-treated patients and more frequently than on placebo) were injection site reactions, nausea, headache, fatigue, thrombocytopenia, and fever.

### DRUG INTERACTIONS

Because of the risk of thrombocytopenia, glomerulonephritis, and renal toxicity, caution should be used when using antiplatelet drugs, anticoagulants, nephrotoxic drugs, and other drugs that may impair renal function concomitantly with TEGSEDI.



**Tegsedi**®  
(inotersen) injection  
284 mg/1.5 mL

Abbreviations: ATTR, transthyretin-mediated amyloidosis; TTR, transthyretin.

Reference: 1. TEGSEDI [package insert]. Boston, MA: Akcea Therapeutics, Inc; 2020.

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## TEGSEDI® (inotersen) injection, for subcutaneous use

Brief summary of Full Prescribing Information. See Full Prescribing Information for complete product information.

### WARNING: THROMBOCYTOPENIA AND GLOMERULONEPHRITIS

#### **Thrombocytopenia**

TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, which can be life-threatening. One clinical trial patient died from intracranial hemorrhage.

TEGSEDI is contraindicated in patients with a platelet count below  $100 \times 10^9/L$  [see *Contraindications (4)* and *Warnings and Precautions (5.2)* of Full Prescribing Information].

Prior to starting TEGSEDI, obtain a platelet count [see *Dosage and Administration (2.3)* of Full Prescribing Information]. During treatment, monitor platelet counts weekly if values are  $75 \times 10^9/L$  or greater, and more frequently if values are less than  $75 \times 10^9/L$  [see *Dosage and Administration (2.4)* and *Warnings and Precautions (5.1)* of Full Prescribing Information].

If a patient develops signs or symptoms of thrombocytopenia, obtain a platelet count as soon as possible. The patient should not receive additional TEGSEDI unless a platelet count is determined to be interpretable and acceptable by a medical professional [see *Warnings and Precautions (5.1)* of Full Prescribing Information].

Following discontinuation of treatment for any reason, continue to monitor platelet count for 8 weeks, or longer if platelet counts are less than  $100 \times 10^9/L$ , to verify that platelet counts remain above  $75 \times 10^9/L$  [see *Dosage and Administration (2.4)* of Full Prescribing Information].

#### **Glomerulonephritis**

TEGSEDI can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. One clinical trial patient who developed glomerulonephritis and did not receive immunosuppressive treatment remained dialysis-dependent. In clinical trials, cases of glomerulonephritis were accompanied by nephrotic syndrome, which can have manifestations of edema, hypercoagulability with venous or arterial thrombosis, and increased susceptibility to infection [see *Warnings and Precautions (5.2)* of Full Prescribing Information].

TEGSEDI should generally not be initiated in patients with urinary protein to creatinine ratio (UPCR) of 1000 mg/g or higher [see *Dosage and Administration (2.4)* and *Warnings and Precautions (5.2)* of Full Prescribing Information].

Prior to starting TEGSEDI, measure the serum creatinine, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), and perform a urinalysis [see *Dosage and Administration (2.3)* of Full Prescribing Information]. During treatment, monitor serum creatinine, eGFR urinalysis, and UPCR every two weeks. TEGSEDI should not be given to patients who develop a UPCR of 1000 mg/g or higher, or eGFR below 45 mL/minute/1.73 m<sup>2</sup>, pending further evaluation of the cause.

If a dose is held, once eGFR increases to  $\geq 45$  mL/minute/1.73 m<sup>2</sup>, UPCR decreases to below 1000 mg/g, or the underlying cause of the decline in renal function is corrected, weekly dosing may be reinitiated. In patients with UPCR of 2000 mg/g or higher, perform further evaluation for acute glomerulonephritis, as clinically indicated. If acute glomerulonephritis is confirmed, TEGSEDI should be permanently discontinued [see *Dosage and Administration (2.4)* and *Warnings and Precautions (5.2)* of Full Prescribing Information].

#### **TEGSEDI REMS Program**

Because of the risks of serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis, both of which require frequent monitoring, TEGSEDI is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the TEGSEDI REMS Program [see *Warnings and Precautions (5.3)* of Full Prescribing Information].

## INDICATIONS AND USAGE

TEGSEDI is a transthyretin-directed antisense oligonucleotide indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults.

## DOSAGE AND ADMINISTRATION

See *Dosage and Administration* and *Warnings and Precautions* of Full Prescribing Information for more information.

**Dosing Information:** The recommended dose of TEGSEDI is 284 mg injected subcutaneously once weekly. For consistency of dosing, patients should be instructed to give the injection on the same day every week.

**Administration:** TEGSEDI is intended for subcutaneous use only. The first injection administered by the patient or caregiver should be performed under the guidance of an appropriately qualified healthcare professional.

**Assessment Prior to Initiating TEGSEDI:** Measure platelet count, serum creatinine, eGFR, UPCR, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin, and perform urinalysis prior to treatment with TEGSEDI and as directed following treatment initiation.

**Laboratory Testing and Monitoring to Assess Safety After Initiating TEGSEDI:** Monitor platelet count, serum creatinine, eGFR, urinalysis, UPCR, ALT, AST, and total bilirubin during treatment with TEGSEDI, and for 8 weeks following discontinuation of treatment. **Platelet count:** Do not initiate TEGSEDI in patients with a platelet count less than  $100 \times 10^9/L$ . If a patient develops signs or symptoms of thrombocytopenia, obtain a platelet count as soon as possible, and hold dosing until platelet count is confirmed. Recheck the platelet count as soon as possible if a platelet measurement is uninterpretable (eg, clumped

sample). During treatment, monitor platelet counts weekly if values are  $75 \times 10^9/L$  or greater, and more frequently if values are less than  $75 \times 10^9/L$  [see *Dosage and Administration* (2.4) and *Warnings and Precautions* (5.1) of Full Prescribing Information]. **Renal monitoring:** TEGSEDI should generally not be initiated in patients with a UPCR of 1000 mg/g or higher. Monitor serum creatinine, eGFR, urinalysis, and UPCR every 2 weeks during treatment with TEGSEDI. Hold TEGSEDI in patients who develop a UPCR of 1000 mg/g or higher, or an eGFR below  $45 \text{ mL/minute/1.73 m}^2$ , pending further evaluation of the cause. If acute glomerulonephritis is confirmed, TEGSEDI should be permanently discontinued. **Liver tests:** Monitor ALT, AST, and total bilirubin every 4 months during treatment with TEGSEDI; monitor monthly for patients who have received a liver transplant [see *Warnings and Precautions* (5.6)].

## CONTRAINDICATIONS

TEGSEDI is contraindicated in patients with a platelet count below  $100 \times 10^9/L$ , a history of acute glomerulonephritis caused by TEGSEDI, or a history of a hypersensitivity reaction to TEGSEDI.

## WARNINGS AND PRECAUTIONS

**Thrombocytopenia:** TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia that can be life-threatening. In Study 1 (the pivotal study) [see *Clinical Studies* (14) of Full Prescribing Information], platelet counts below  $100 \times 10^9/L$  occurred in 25% of TEGSEDI-treated patients compared with 2% of patients on placebo. Platelet counts below  $75 \times 10^9/L$  occurred in 14% of TEGSEDI-treated patients compared with no patients on placebo. Three TEGSEDI-treated patients (3%) had sudden severe thrombocytopenia (platelet count below  $25 \times 10^9/L$ ), which can have potentially fatal bleeding complications, including spontaneous intracranial or intrapulmonary hemorrhage. One patient in a clinical trial experienced a fatal intracranial hemorrhage. Do not initiate TEGSEDI in patients with a platelet count below  $100 \times 10^9/L$ . Follow recommended monitoring and treatment recommendations for platelet count [see *Dosage and Administration* (2.4) of Full Prescribing Information].

**Glomerulonephritis and Renal Toxicity:** TEGSEDI can cause glomerulonephritis that may result in dialysis-dependent renal failure. In Study 1 [see *Clinical Studies* (14) of Full Prescribing Information], glomerulonephritis occurred in 3 (3%) TEGSEDI-treated patients compared with no patients on placebo. In these patients, stopping TEGSEDI alone was not sufficient to resolve manifestations of glomerulonephritis, and treatment with an immunosuppressive medication was necessary. If glomerulonephritis is suspected, pursue prompt diagnosis and initiate immunosuppressive treatment as soon as possible. TEGSEDI-treated patients who develop glomerulonephritis will require monitoring and treatment for nephrotic syndrome and its manifestations. Follow recommended monitoring and treatment recommendations for renal parameters [see *Dosage and Administration* (2.4) of Full Prescribing Information]. TEGSEDI should generally not be initiated in patients with a UPCR of 1000 mg/g or greater. If acute glomerulonephritis is confirmed, TEGSEDI should be permanently discontinued [see *Contraindications* (4) of Full Prescribing Information].

**TEGSEDI REMS:** TEGSEDI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TEGSEDI REMS Program because of risks of serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis [see *Warnings and Precautions* (5.1, 5.2) of Full Prescribing Information].

**Stroke and Cervicocephalic Arterial Dissection:** TEGSEDI may cause stroke and cervicocephalic arterial dissection. In clinical studies, 1 of 161 (0.6%) TEGSEDI-treated patients experienced carotid artery dissection and stroke. Educate patients on the symptoms of stroke and central nervous system arterial dissection. Instruct patients to seek help as soon as possible if symptoms of stroke or arterial dissection occur.

**Inflammatory and Immune Effects:** Inflammatory and immune changes are an effect of some antisense oligonucleotide drugs, including TEGSEDI. In clinical studies, serious inflammatory and immune adverse reactions occurred in TEGSEDI-treated patients, including immune thrombocytopenia and glomerulonephritis, as well as a single case of antineutrophil cytoplasmic autoantibody (ANCA)-positive systemic vasculitis [see *Warnings and Precautions* (5.2, 5.3) of Full Prescribing Information].

**Liver Injury:** In clinical studies, 8% of TEGSEDI-treated patients had an increased alanine aminotransferase (ALT) at least 3 times the upper limit of normal (ULN) compared with 3% of patients on placebo; 3% of TEGSEDI-treated patients had an ALT at least 8 times the ULN compared with no patients on placebo. Monitor ALT, aspartate aminotransferase, and total bilirubin at baseline and every 4 months during treatment with TEGSEDI. If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction, promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with TEGSEDI, as appropriate.

**Liver Transplant Rejection:** In a clinical study, cases of liver transplant rejection were reported 2-4 months after starting TEGSEDI in patients whose liver allografts had previously been clinically stable (for over 10 years) prior to starting TEGSEDI. In these cases, the patients clinically improved and transaminase levels normalized after glucocorticoid administration and cessation of TEGSEDI. In patients with a history of liver transplant, monitor ALT, AST, and total bilirubin monthly. Discontinue TEGSEDI in patients who develop signs of liver transplant rejection.

**Hypersensitivity Reactions/Antibody Formation:** TEGSEDI can cause hypersensitivity reactions. In clinical studies, 6 of 161 (4%) TEGSEDI-treated patients stopped treatment because of a hypersensitivity reaction. These reactions generally occurred within 2 hours of administration of TEGSEDI. Antibodies to TEGSEDI were present when the reactions occurred. If a hypersensitivity reaction occurs, discontinue administration of TEGSEDI and initiate appropriate therapy. Do not use in patients who have a history of hypersensitivity reactions to TEGSEDI.

**Uninterpretable Platelet Counts: Reaction Between Antiplatelet Antibodies and Ethylenediaminetetraacetic Acid (EDTA):** In Study 1 [see *Clinical Studies* (14) of Full Prescribing Information], 23% of TEGSEDI-treated patients had at least 1 uninterpretable platelet count caused by platelet clumping compared with 13% of patients on placebo. If there is suspicion of EDTA-mediated platelet clumping, perform a repeat platelet count using a different anticoagulant (eg, sodium citrate, heparin) in the blood collection tube. Recheck the platelet count as soon as possible if a platelet measurement is uninterpretable. Hold TEGSEDI dosing until an acceptable platelet count is confirmed with an interpretable blood sample.

**Reduced Serum Vitamin A Levels and Recommended Supplementation:** TEGSEDI treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A is advised for patients taking TEGSEDI. Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (eg, night blindness).

## ADVERSE REACTIONS

See boxed **WARNING** and **Warnings and Precautions** of Full Prescribing Information for additional serious adverse reactions.

**Clinical Trials Experience:** A total of 112 adult patients with polyneuropathy caused by hATTR amyloidosis received TEGSEDI in Study 1 and 60 patients received placebo. The mean exposure to TEGSEDI was 385 days, and the median exposure was 449 days.

The table to the right presents common adverse reactions that occurred in at least 5% of TEGSEDI-treated patients and that occurred at least 5% more frequently or 2 times more frequently than on placebo. Serious adverse reactions were more frequent in TEGSEDI-treated patients (32%) than in patients on placebo (21%). The most common adverse reactions leading to discontinuation were thrombocytopenia and cachexia.

**Immunogenicity:** In Study 1, 30% of TEGSEDI-treated patients tested positive for anti-drug antibodies (ADA) following 65 weeks of treatment [see **Warnings and Precautions** (5.7, 5.8) of Full Prescribing Information]. However, the assay measured only IgG isotypes and the existence of other isotypes may be possible. In many cases adverse reactions occurred in patients with ADA, although the available data are too limited to make definitive conclusions about the relationship. See **Adverse Reactions** and **Warnings and Precautions** of Full Prescribing Information for additional information.

## DRUG INTERACTIONS

**Antiplatelet Drugs or Anticoagulant Medications:** Because of the risk of thrombocytopenia, caution should be used when using antiplatelet drugs, including non-prescription products that affect platelets, or anticoagulants, concomitantly with TEGSEDI [see **Warnings and Precautions** (5.1) of Full Prescribing Information].

**Nephrotoxic Drugs:** Because of the risk of glomerulonephritis and renal toxicity, caution should be used when using nephrotoxic drugs and other drugs that may impair renal function concomitantly with TEGSEDI [see **Warnings and Precautions** (5.2) of Full Prescribing Information].

## USE IN SPECIFIC POPULATIONS

### Pregnancy

**Pregnancy Exposure Registry:** There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to TEGSEDI during pregnancy. Health care providers are encouraged to register patients and pregnant women are encouraged to register themselves by calling: 1-877-465-7510, emailing: tegsedipregnancy@ubc.com, or visiting online at: www.tegsedipregnancystudy.com.

There are no data on the developmental risk associated with the use of TEGSEDI in pregnant women. TEGSEDI treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for patients taking TEGSEDI. Vitamin A is essential for normal embryofetal development; however, excessive levels of vitamin A are associated with adverse developmental effects. The effects on the fetus of a reduction in maternal serum TTR caused by TEGSEDI and of vitamin A supplementation are unknown [see **Clinical Pharmacology** (12.2) and **Warnings and Precautions** (5.9) of Full Prescribing Information].

**Lactation:** There is no information regarding the presence of TEGSEDI in human milk, the effects on the breast-fed infant, or the effects on milk production. A study in lactating mice has shown excretion of inotersen in milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for TEGSEDI and any potential adverse effects on the breastfed infant from TEGSEDI or from the underlying maternal condition.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use:** Clinical studies of TEGSEDI included 69 patients (45%) aged 65 and over. No differences in pharmacokinetics or effectiveness were observed between these patients and younger patients. Patients 65 years and older may be at increased risk of certain adverse reactions, such as congestive heart failure, chills, myalgia, and extremity pain.

**Renal Impairment:** No dose adjustment is necessary in patients with mild to moderate renal impairment (eGFR  $\geq 30$  to  $< 90$  mL/min/1.73 m<sup>2</sup>) [see **Clinical Pharmacology** (12.3) of Full Prescribing Information]. TEGSEDI has not been studied in patients with severe renal impairment or end-stage renal disease.

**Hepatic Impairment:** No dose adjustment is necessary in patients with mild hepatic impairment [see **Clinical Pharmacology** (12.3) of Full Prescribing Information]. TEGSEDI has not been studied in patients with other degrees of hepatic impairment.

**For detailed information, please see full Prescribing Information.**

**For more information about TEGSEDI, visit [www.TEGSEDIhcp.com](http://www.TEGSEDIhcp.com) or call 1-844-483-4736.**

## Adverse Reactions Reported in at Least 5% TEGSEDI-Treated Patients and That Occurred at Least 5% More Frequently or at Least 2 Times More Frequently Than Placebo Patients (Study 1)

	TEGSEDI (N=112) %	PLACEBO (N=60) %
Injection site reactions <sup>a</sup>	49	10
Nausea	31	12
Headache	26	12
Fatigue	25	20
Thrombocytopenia	24	2
Fever	20	8
Peripheral edema	19	10
Chills	18	3
Anemia	17	3
Vomiting	15	5
Myalgia	15	10
Decreased renal function	14	5
Arrhythmia <sup>b</sup>	13	5
Arthralgia	13	8
Pre-syncope or syncope	13	5
Decreased appetite	10	0
Paresthesia	10	3
Dyspnea	9	3
Elevated liver function test	9	3
Orthostasis	8	2
Influenza-like illness	8	3
Contusion	7	2
Bacterial infection <sup>c</sup>	7	3
Eosinophilia	5	0
Dry mouth	5	2

<sup>a</sup>Includes bruising, erythema, hematoma, hemorrhage, induration, inflammation, mass, edema, pain, pruritus, rash, swelling, and urticaria.

<sup>b</sup>Includes arrhythmia, atrial fibrillation, atrial flutter, bradyarrhythmia, bradycardia, extrasystoles, sinus arrhythmia, sinus bradycardia, supraventricular extrasystoles, tachycardia, and ventricular extrasystoles.

<sup>c</sup>Includes bacteremia, cellulitis staphylococcal, clostridium difficile infection, conjunctivitis bacterial, cystitis *Escherichia*, *Helicobacter* gastritis, *Helicobacter* infection, Staphylococcal infection.

**(CONTINUED FROM PAGE 1)**

Kenney also emphasized the importance of agreement between the 2 parties on the selected outcome measure. “If we miss something in the negotiation or in the design, and maybe we didn’t have all the information we needed to appropriately assess the outcome, you can certainly make an adjustment,” he said. “But that really should be resolved during that 4-step process.”

Physician resistance or the need to change behavior could also be an issue, according to Kenney, although he said that physicians should be supportive of the goal to drive improved outcomes. The realization of savings and benefits is also important to consider, and Kenney noted that in some cases, the overall outcomes can be positive; even if the contract does not perform well from a financial perspective, clinical outcomes might be achieved. Furthermore, the willingness of the manufacturer to negotiate is another important consideration that varies among pharmaceutical companies, according to Kenney.

## EXPERIENCE WITH VBAs IN RARE DISEASE

Approximately two-thirds of the panelists said that their respective organizations have implemented at least 1 VBA, and approximately half said that they have worked with 1 or more rare disease VBAs, most of which lasted 1 to 3 years. **Erik Schindler, PharmD**, director of emerging therapeutics and outcomes-based contracting at UnitedHealthcare in Ballwin, Missouri, added that assessment of the level of risk and value is particularly important with VBAs for rare disease therapies. “Ideally, you don’t want to encounter a failure, but if that failure’s provided significant protection, you’ll engage that,” he said.

**Peter Neumann**, director of the Center for the Evaluation of Value and Risk in Health at Tufts Medical Center in Boston, Massachusetts, added that there is a “sweet spot” for the amount of uncertainty in an agreement and emphasized that VBAs generally work better with “hard” end points, such as mortality or cardiac events, or a good biomarker. However, he cautioned that there is little formal research that has evaluated whether patient outcomes are improved with VBAs compared with an alternative arrangement.

**Bhavesh Shah, RPh**, senior director of specialty and hematology/oncology pharmacy at Boston Medical Center Health System, pointed out that clinically meaningful and durable outcomes are also important for a successful VBA. “When you have a product where you have response as an outcome but

that response is not durable, then it’s really not a VBA agreement that we want to do, especially when, within 6 months, half of your patients are going to relapse,” he said.

As for the optimal time to start discussions, Shah said that he initiates discussions about therapies while the agents are being studied in clinical trials, and Schindler said that discussions may start 12 to 18 months before approval of pipeline medications, if the early data are promising. However, Schindler also noted that information on outcomes may be limited and that the pharmaceutical manufacturer may be hesitant to go into the details of the contract, finances, and implications of the clinical trial findings.

**Bruce Nash, MD**, former chief physician executive of Blue Cross Blue Shield of Massachusetts in Boston and Schindler both pointed out that approvals for drugs targeting orphan diseases are often accelerated with small data sets, which may increase hesitancy among commercial plan sponsors, and they suggested that safeguards should be provided in the VBA to protect against negative outcomes.<sup>3</sup> “I have been in a situation where I’ve been talking to commercial plan sponsors and they understand the potential value, but they can’t wrap their heads around the financial extremes,” said Schindler. “And just like in many other situations, there could be people that may appreciate the minutiae of a disease or the minutiae of the clinical aspect, but they make decisions outside of that.”

He added that a well-designed, outcomes-based contract that assures efficacy and protects against negative outcomes can help in this situation. “The last thing these plans want to do is spend this much a month, and 30 days later, find out it didn’t work or, in some cases where multiple agents are in a disease state, to pay for the medication only to have subsequent expenditures for an alternative therapy shortly thereafter,” said Schindler.

**Ryan Bitton, PharmD, MBA**, senior director of pharmacy services for Health Plan of Nevada in Las Vegas, also noted that outcomes in rare diseases are often more patient based and focused on disease control than those in common diseases, which are often focused on cost savings. He claimed that even the studies that have been conducted may have been based on less than ideal end points. “I think that’s not the ideal of where we want to be from a health plan perspective,” said Bitton.

The panelists added that they have limited ability to negotiate value and costs in rare diseases, in part

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because of the relatively small number of competitive products in the same arena. However, Shah noted that products may overlap in some cases, which provides an opportunity for negotiation of VBAs. **Gary Tesero, PharmD, RPh**, director of pharmacy and case management services at Health New England in Springfield, Massachusetts, added that the large volume of requests from manufacturers with rare disease products in clinical trials can become overwhelming to payers, and payers need to assess their medical claims data to ensure they have a sufficient number of patients with the rare disease to make it worth pursuing the VBA.

“Obviously the penetrance of this gene is not 100%...but we don’t really know what the penetrance is, so we don’t really know how many of these patients have amyloidosis due to this gene.”

— Sami Khella, MD

**Shawn Barger, PharmD**, director of pharmacy at AvMed Health Plans in Gainesville, Florida, said that small integrated health plans may have more clout if they approach manufacturers as a group and pool their resources, particularly for rare disease agents. “Some of us may not have a member who has one of these diseases today, but we could next year,” said Barger.

Kenney also suggested the idea of offering VBAs to large employers to ensure appropriate use and value-based pricing to employees, but Bitton and Tesero noted that interest among employers has been low.

## OVERVIEW OF hATTR AMYLOIDOSIS

### *Prevalence and Diagnosis*

As a multisystemic and multigenotypic disease, hATTR amyloidosis develops from the deposition of insoluble amyloid fibrils throughout multiple organs and tissues, including those of the nervous system.<sup>4,5</sup> Although the disease is rare, it is thought to be underdiagnosed because the symptoms are nonspecific, and diagnosis relies on the detection of amyloid in a tissue biopsy.<sup>5</sup> Transthyretin is a 127–amino acid, 55-kDa protein that is expressed primarily in the liver. It normally exists as a homotetramer but can disassociate into alternatively folded monomeric intermediates that self-assemble into amyloid fibrils as a result of genetic mutations or aging.<sup>4</sup> Amyloid deposition commonly occurs in the nervous system and myocardium, leading to polyneuropathy, cardiomyopathy, and heart failure.<sup>4</sup> The predominant clinical manifestation (polyneuropathy

or cardiomyopathy) often determines the categorization of hATTR amyloidosis,<sup>5</sup> although the majority of *TTR* mutations are associated with a mixed clinical phenotype.<sup>5</sup>

Although Khella claimed that epidemiologic estimates suggest the existence of approximately 50,000 cases of hATTR amyloidosis worldwide, he predicted that there are likely many more cases that are either unrecognized or misdiagnosed by providers. The disease appears to be endemic in the United States, Brazil, Portugal, Sweden, and Japan, with a small number of cases scattered throughout the European Union.

Other characteristics of hATTR amyloidosis include an autosomal dominant inheritance pattern with widely variable penetrance and age of onset.<sup>6</sup> Khella presented an analysis of patients with cardiac symptoms in the Pfizer Transthyretin-Associated Amyloidosis Outcome Survey (THAOS) database, which showed that approximately half of all patients in the United States with ATTR were *TTR* wild type, whereas 23% had the Val122Ile mutation. This mutation is more frequent in the African American population (3% to 3.9%) than in White or Hispanic populations in the United States (0.44% and 0%, respectively) and leads to late-onset cardiac amyloidosis in most patients.<sup>6</sup> Khella estimated that 1.6 million African Americans carry the Val122Ile mutation based on this estimated prevalence. “Obviously the penetrance of this gene is not 100%...but we don’t really know what the penetrance is, so we don’t really know how many of these patients have amyloidosis due to this gene,” he said.

In addition, the median survival after development of cardiomyopathy was shown to be shorter in patients with the Val122Ile mutation than in those with wild-type *ATTR* in the Transthyretin Amyloidosis Cardiac Study (25.6 vs 43.0 months).<sup>4</sup> This emphasizes the importance of identifying patients with the Val122Ile mutation.

Khella added that the neuropathy associated with hATTR amyloidosis is similar to (and often misdiagnosed as) chronic inflammatory demyelinating polyneuropathy (CIDP). Both conditions can present with proximal weakness, although polyneuropathy associated with hATTR amyloidosis is often accompanied by autonomic symptoms, such as diarrhea and constipation. The polyneuropathy associated with hATTR amyloidosis is categorized into 3 stages of familial amyloidotic polyneuropathy (FAP). The first stage is characterized by normal functioning in daily activities and mild neuropathy in the lower extremities. Progression of motor signs in the lower limbs and weakening of hand muscles occur in the second stage, and patients in the third stage who use a wheelchair and have generalized weakness and areflexia.<sup>7</sup> Khella also pointed out that the progressive nature is another key feature distinguishing amyloid polyneuropathy from CIDP, with the average duration of 5.6, 4.8, and 2.3 years in the first, second, and third stages of FAP, respectively.<sup>7</sup>

When performing a work-up on a patient with progressive neuropathy, Khella said that he performs genetic testing and obtains a biopsy of skin or fat. A positive biopsy and negative genetic test results indicate wild-type *ATTR* or light chain amyloidosis. Positive genetic testing indicates that the patient is a carrier of hATTR amyloidosis. A positive biopsy further indicates a presence of the disease in these

patients. Khella recommended annual follow-up of known carriers with prompt treatment of hereditary amyloidosis. Currently, biopsy is not among required Utilization Management criteria for most payers due to accessibility of testing, pathology, and variability of results outside an institutional/teaching hospital setting.

### Emerging hATTR Therapies

Currently, approved treatments for hATTR amyloidosis are focused on stabilizing the TTR tetramer or reducing the production of TTR from the liver through gene silencing. Inotersen (Tegsedi) is a transthyretin-directed antisense oligonucleotide, approved in 2018 and administered weekly via subcutaneous injection, and available through the Tegsedi Risk Evaluation and Mitigation Strategy Program for adults with hATTR amyloidosis presenting with polyneuropathy.<sup>8</sup> Patisiran (Onpattro) is another TTR gene silencer (via a TTR-directed small interfering RNA) administered intravenously every 3 weeks, which was approved in 2018 for the treatment of polyneuropathy associated with hATTR amyloidosis.<sup>9</sup> Tafamidis (Vyndaqel/Vyndamax) is an oral TTR tetramer stabilizer approved in 2019 for the treatment of cardiomyopathy in patients with wild-type or hereditary ATTR.<sup>10</sup> However, Khella noted that it is not approved in the United States for the treatment of polyneuropathy associated with hATTR amyloidosis.

### Neurologic Examination

The Neuropathy Impairment Score (NIS) is a scoring system used for the ongoing evaluation of patients in various clinical trials and epidemiologic studies.<sup>11</sup> The modified NIS + 7 (mNIS + 7) score was specifically developed to assess polyneuropathy-related impairment in patients with hATTR amyloidosis.<sup>11</sup> The Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire has also been used as an end point in clinical trials, to assess activities of daily living, physical functioning/large fiber neuropathy, autonomic neuropathy, symptoms, and small-fiber neuropathy.<sup>12</sup> A higher total quality-of-life score is associated with more severe disease in patients with hATTR amyloidosis.<sup>12</sup> However, Khella pointed out that motor strength and physical functioning account for the majority of the NIS and Norfolk QOL-DN scales, respectively; thus, these may not be highly accurate in measuring outcomes of neuropathy in Val122Ile-mutated hATTR amyloidosis, which primarily manifests as sensory neuropathy. “For these patients, the motor part of the scale may not change a whole lot,” said Khella. “For you guys who are doing these value-based measurements, you have to be careful what you ask and how you assess the efficacy of the drug based on some kind of a scale.” Khella suggested PND Scoring or FAP staging as alternatives to NIS, mNIS + 7, and Norfolk QoL-DN methodologies, which are primary used in clinical trials but not routinely used in clinical practice.

Nevertheless, Khella said that the phase 3 trials of inotersen (NEURO-TTR; NCT01737398) and patisiran (APOLLO; NCT01960348) showed robust differences between the treatment and placebo groups in the progression of mNIS + 7 and Norfolk QOL-DN scores over study periods of 66 weeks (NEURO-TTR) and 18 months (APOLLO), with

all subgroups of patients appearing to benefit from treatment.<sup>13,14</sup> Follow-up data also indicate that early initiation of treatment has a significant effect on long-term outcomes. An open-label extension study (NCT02175004) that included participants who completed the NEURO-TTR trial (97% of patients who completed the NEURO-TTR trial enrolled in the open-label extension study) showed that patients who switched from placebo to inotersen showed improvement or stabilization in mNIS + 7, Norfolk QOL-DN, and 36-Item Short Form Health Survey—physical component summary scores compared with predicted worsening with placebo.<sup>15</sup> However, Khella pointed out that these patients tended to have higher mNIS + 7 scores after 104 weeks than patients who received inotersen in the NEURO-TTR trial.<sup>15</sup> “The ground that you lose [in treatment of the disease] is lost forever,” said Khella.

Khella added that hATTR amyloidosis often remains undiagnosed for 3 years or longer, at which point the disease is often advanced. “I think about a quarter of patients will have seen about 5 physicians or health care providers before they reach somebody who makes a diagnosis,” said Khella. “It continues to be a real challenge in the community because the disease looks like every other neuropathy in the beginning. The difference is that this becomes an impairing neuropathy, rather than just the basic old numbness and tingling that you see in most neuropathies.”

Inotersen and patisiran were generally safe in the trials, with most adverse events of mild to moderate severity. Glomerulonephritis occurred in 3 patients who received inotersen in the international, randomized, double-blind, placebo-controlled, phase 3 NEURO-TTR trial (NCT01737398).<sup>13</sup> All 3 patients were carriers of the Val30Met mutation, among which 2 showed a decline in the estimated glomerular filtration rate.<sup>13</sup> A larger proportion of the inotersen group showed a reduced platelet count after baseline, to less than 140,000/mm<sup>3</sup> compared with the placebo group (54% vs 13%).<sup>13</sup> However, Khella said that very few patients need to switch from inotersen to patisiran because of their platelet count and can often tolerate inotersen after a drug holiday of 1 to 2 weeks. Patisiran was similarly well tolerated in the international, randomized, double-blind, placebo-controlled, phase 3 APOLLO trial, with peripheral edema and infusion-related reactions being the only adverse events occurring more frequently with patisiran than with placebo.<sup>14</sup>

## VBA<sub>s</sub> IN hATTR AMYLOIDOSIS

The panelists all considered agents for cardiomyopathy and polyneuropathy to be in 2 separate classes for hATTR amyloidosis. However, many said that they do not have a straightforward method of identifying patients with hATTR amyloidosis because there is often no specific code in the *International Classification of Diseases, Tenth Revision* for the disease or a breakdown of the predominant symptom (cardiomyopathy or peripheral neuropathy). Although **Steven Evans, MD**, vice president of quality and utilization management at Intermountain Healthcare in Las Vegas, estimated that 10 members of a 1-million-member plan would have hATTR amyloidosis, Shah said that getting

an accurate estimate is difficult because of the delays in diagnosis. However, Shah added that new guidelines from the American Heart Association, which provide instructions on diagnostics for hATTR amyloidosis, may help improve diagnosis. Furthermore, Khella agreed that he has recently seen an uptick of patients with hATTR amyloidosis. This is likely related to patients and their families becoming increasingly familiar with the condition and the improvements in diagnostic capabilities among health care providers.

Despite their clinical efficacy, patisiran and inotersen are not cost-effective; a 2018 analysis by the Institute for Clinical and Economic Review (ICER) showed that the long-term cost-effectiveness of patisiran was \$850,000 per quality-adjusted life-year (QALY) gained compared with the best supportive care, which was much higher than commonly accepted thresholds of \$50,000 to \$150,000 per QALY.<sup>16</sup> Similarly, the 2018 report from ICER showed that inotersen, discounted at 3%, had an incremental cost-effectiveness of \$1.73 million per QALY.<sup>17</sup> However, Neumann said that a key limitation of cost-effectiveness analysis is the general omission of the costs associated with the diagnostic process, which is an important consideration in hATTR amyloidosis. He added that identifying and treating patients early in the disease course could be particularly beneficial for those “who would otherwise [have] gone on a diagnostic odyssey.”

**There’s more work that needs to be done from a real-world perspective, if you really want to have VBAs [value-based agreements] that are meaningful and measurable in clinical practice from a payer’s perspective and a provider’s perspective.**

— Bhavesh Shah, RPh

As for utilization management strategies with high-priced rare disease agents, Schindler said that his group aims to align utilization with the evidence “on top of the label” and according to the evidence presented. This can be achieved, for example, by limiting the use of combination treatments that have minimal supporting evidence and/or are extremely expensive. He added that consideration of the patient’s FAP staging is important for utilization management in neurodegenerative diseases such as hATTR amyloidosis because a patient with FAP stage III disease may derive minimal benefit. In general, panelists said that renewal criteria are in their plans and are specific to each agent. However, Shah noted that with the advent of coronavirus disease 2019, some of the payers have modified renewal

policies, such as requiring neither reauthorizations nor weekly platelet monitoring for patients with hATTR amyloidosis.

Structuring VBAs for hATTR amyloidosis remains a challenge. According to Barger, key factors contributing to difficulties associated with VBAs include the lack of clinical implementation of validated scores used for assessment in clinical trials and the lack of a requirement for practitioners to monitor patients in a standardized manner. Tesero said that consulting with a neurologist can provide education about the benefits of each agent from a cost and patient standpoint, which may help identify clinically relevant outcome measures to include in a VBA. Shah suggested that the use of multiple measures of functional status and cardiac biomarkers in a VBA for hATTR amyloidosis agents may be feasible from a clinical standpoint. Again, Khella added that assessment of polyneuropathy disability stage may be a clinically practical measurement for neurologists, as most do not use the NIS.

Regarding follow-up measures for reauthorization of the approved hATTR amyloidosis agents, Khella noted that although the condition of patients generally continues to progress, the rate of progression is slower with treatment. He also noted that slowly progressing disease is not necessarily an indication of ineffective treatment. “Having treated these patients for 25 or more years, [I know that] they relentlessly get worse,” said Khella. He noted that hATTR amyloidosis agents can stabilize the condition in patients. “While they may get a little bit worse, and I definitely have patients getting worse, I suspect that their pace of deterioration would’ve been a lot worse...if they weren’t on the drugs.”

Nash pointed out that the duration of progression of hATTR amyloidosis (often several years) generally exceeds the duration of most VBA contracts (1-3 years). Furthermore, several payers cautioned that the difficulty in predicting disease progression that would occur without the new hATTR amyloidosis agents makes it difficult to get an accurate assessment of their cost-effectiveness. Schindler noted that stabilization or improvement of the modified NIS score after a single assessment of a patient would provide useful information. Conversely, he noted that if that patient was evaluated and showed an increase of 20 (in the modified NIS score) over time, they probably would have declined further. However, Schindler stated that “the question is, can we appreciably quantify the benefit that the declining patient is getting, relative to the one who’s stabilized?”

Although regulatory approval for agents outside the US may influence access to treatments for rare diseases such as hATTR amyloidosis, Tesero said that this would generally represent unique situations considered to be exceptions to the rule. “In general, [the] majority of our approval and management ends up being based on data that [are] within the United States and...the FDA,” said Tesero.

## CLOSING REMARKS

The participants concluded that although VBAs have become increasingly popular among payers and manufacturers, the short duration of the contracts, rare/small and unpredictable patient populations,

lack of established/measurable objective outcomes, and high drug costs do not make conventional VBAs well suited for agents used to treat hATTR amyloidosis. However, alternative prevalence, indication-based, or more “traditional” utilization rebate-based contracting strategies may be more readily achievable and are routinely being discussed between payers and manufacturers in this space. “There is a certain appeal to these value-based contracts in a sense that it promises—conceptually, at least—that we’ll target resources better for patients when the drug works, and we won’t pay when the drug doesn’t work, or we’ll pay more when the drug works,” said Neumann. “The problem is...how do you know if something is really working in a nonrandomized environment, especially when the end points used in the trials are not [reflecting] real-world [data] and aren’t enough?...Drug companies could just lower their prices, but what price is appropriate? It’s hard to know.” Tesero added that knowing when to initiate or discontinue these agents is important for value-based discussions, as is promoting the consideration of outcome measures used in clinical trials, such as the NIS, among providers.

Shah concluded that because of the debilitating nature of hATTR amyloidosis, finding ways in which to pay for agents and being able to tie measurable outcomes to a VBA are essential for early and effective patient management. “If there is a way to actually look at what happens to a patient, a total cost of care model...if they do have this drug...we could probably learn a lot from this real-world evidence, beyond the trial outcomes that we see,” said Shah. “There’s more work that needs to be done from a real-world perspective, if you really want to have VBAs that are meaningful and measurable in clinical practice from a payer’s perspective and a provider’s perspective.” •

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