

Akcea announces approval for reimbursement of TEGSEDI® (inotersen) in Italy for treatment of hereditary transthyretin amyloidosis with polyneuropathy
TEGSEDI is the first antisense oligonucleotide medicine available to hATTR patients with polyneuropathy in Italy for at-home subcutaneous injection

BOSTON, June 8, 2020 /PRNewswire/ -- Akcea Therapeutics, Inc. (NASDAQ: AKCA), a majority-owned affiliate of Ionis Pharmaceuticals, Inc., today announced that AIFA, or The Italian Medicines Agency, has granted approval for the reimbursement of TEGSEDI® (inotersen) for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin (hATTR) amyloidosis.

"The approval of reimbursement for TEGSEDI in Italy is an exciting milestone as people living with hATTR amyloidosis with polyneuropathy will now have a much-needed treatment option available, and one that can be administered at home," said Michael Pollock, SVP, head of Europe at Akcea.

"We are pleased that following the Italian Medicines Agency's detailed evaluation of TEGSEDI they are recognizing the serious unmet need of hATTR amyloidosis patients in the Country and the significance of the safety and efficacy data demonstrated thus far from this therapy, including positive long-term results from the NEURO-TTR open-label extension study that were recently published in the *European Journal of Neurology*," said Massimo Boriero, VP, general manager of Italy at Akcea. "We look forward to continue to work with the Italian Medicines Agency to rapidly bring TEGSEDI to appropriate patients."

hATTR amyloidosis is an under-recognized, debilitating and progressive disease that is caused by the buildup of TTR proteins that misfold due to inherited genetic mutations. It is characterized by the deposition of amyloid fibrils throughout the body including in nervous tissue and can have a devastating impact on patients' quality of life.

TEGSEDI is a once-weekly, at-home subcutaneous injection that targets the polyneuropathy of hATTR amyloidosis at its source by silencing the defective gene in these patients and reducing abnormal production of the TTR protein. It is the first antisense oligonucleotide medicine available for patients in Italy with hATTR amyloidosis with polyneuropathy, and also the first treatment available to Italian patients that can be self-administered at home.

"hATTR is a complex disease and we understand how important it is for patients to have access to treatment as soon as possible as the disease can quickly progress. TEGSEDI is an important treatment option for the hATTR community, and long-term data shows that patients treated with TEGSEDI continue to experience improvements in measures of neuropathy and quality of life, with greater effects seen when treatment is started earlier in the disease lifecycle," said Laura Obici, M.D., Fondazione IRCCS Policlinico San Matteo.

The Italian Medicines Agency's approval of reimbursement for TEGSEDI was based on results from the Phase 3 NEURO-TTR study in patients with hATTR amyloidosis with symptoms of polyneuropathy. Results from that study demonstrated that patients treated with TEGSEDI experienced significant benefit compared to patients treated with placebo across both co-primary endpoints: the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN) and modified Neuropathy Impairment Score +7 (mNIS+7), a measure of neuropathic disease progression.

In 2018, TEGSEDI was the first RNA-targeted therapeutic approved by the European Commission for adult patients with hATTR amyloidosis. Since then, TEGSEDI has continued to receive regulatory and reimbursement approvals across Europe and is now commercially available in 13 countries.

ABOUT TEGSEDI® (INOTERSEN)

TEGSEDI was approved by the U.S. Food and Drug Administration (FDA) for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults. TEGSEDI, discovered and developed by Ionis Pharmaceuticals, is the world's first and only subcutaneous RNA-targeting drug designed to reduce the production of human transthyretin (TTR) protein. TEGSEDI also received marketing authorization in the European Union and Canada for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis.

The approval is based on data from the NEURO-TTR study that was a Phase 3 randomized (2:1), double-blind, placebo-controlled, 15-month, international study in 172 patients with hATTR amyloidosis with symptoms of polyneuropathy. In NEURO-TTR, TEGSEDI demonstrated significant improvement compared to placebo in measures of neuropathy and quality of life as measured by the modified Neuropathy Impairment Score +7 (mNIS+7) and in the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QOL-DN) total score. Patients treated with TEGSEDI experienced similar benefit regardless of subgroups such as age, sex, race, region, Neuropathy Impairment Score (NIS), Val30Met mutation status, and disease stage.

The approval is also based on data from the NEURO-TTR Open Label Extension (OLE) that is an ongoing study for patients who completed the NEURO-TTR study, designed to evaluate the long-term efficacy and safety of TEGSEDI.

For TEGSEDI's full prescribing information, please visit www.TEGSEDI.com.

IMPORTANT SAFETY INFORMATION

BOXED 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 100×10^9 /L**
- **Prior to starting TEGSEDI, obtain a platelet count. During treatment, monitor platelet counts weekly if values are 75×10^9 /L or greater, and more frequently if values are less than 75×10^9 /L**
- **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**
- **Following discontinuation of treatment for any reason, continue to monitor platelet count for 8 weeks, or longer if platelet counts are less than normal, to verify that platelet counts remain above 75×10^9 /L**

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**
- **TEGSEDI should generally not be initiated in patients with urinary protein to creatinine ratio (UPCR) of 1000 mg/g or higher**

- **Prior to starting TEGSEDI, measure the serum creatinine, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), and perform a urinalysis. During treatment, monitor serum creatinine, eGFR urinalysis, and UPCR every 2 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 m², pending further evaluation of the cause**
- **If a dose is held, once eGFR increases to ≥ 45 mL/minute/1.73 m², 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**

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**

CONTRAINDICATIONS

TEGSEDI is contraindicated in patients with

- Platelet count below 100×10^9 /L
- History of acute glomerulonephritis caused by TEGSEDI
- 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, platelet counts below 100×10^9 /L occurred in 25% of TEGSEDI-treated patients compared with 2% of patients on placebo. Platelet counts below 75×10^9 /L occurred in 14% of TEGSEDI-treated patients compared with no patients on placebo. One patient in a clinical trial experienced a fatal intracranial hemorrhage. Do not initiate TEGSEDI in patients with a platelet count below 100×10^9 /L. Follow recommended monitoring and treatment recommendations for platelet count.

Symptoms of thrombocytopenia can include unusual or prolonged bleeding (eg, petechiae, easy bruising, hematoma, subconjunctival bleeding, gingival bleeding, epistaxis, hemoptysis, irregular or heavier than normal menstrual bleeding, hematemesis, hematuria, hematochezia, melena), neck stiffness, or atypical severe headache. Patients and caregivers should be instructed to be vigilant for symptoms of thrombocytopenia and seek immediate medical help if they have concerns.

Glomerulonephritis and Renal Toxicity

TEGSEDI can cause glomerulonephritis that may result in dialysis-dependent renal failure. In Study 1, glomerulonephritis occurred in 3 (3%) TEGSEDI-treated patients compared with no patients on placebo. One patient did not receive immunosuppressive treatment and remained dialysis-dependent. If glomerulonephritis is suspected, pursue prompt diagnosis and initiate immunosuppressive treatment as soon as possible. Follow recommended monitoring and treatment recommendations for renal parameters. 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.

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.

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.

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, 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

The most common adverse reactions that occurred in at least 20% of TEGSEDI-treated patients and more frequently than in those on placebo were injection site reactions, nausea, headache, fatigue, thrombocytopenia, and fever. Serious adverse reactions were more frequent in TEGSEDI-treated patients (32%) than in patients on placebo (21%).

DRUG INTERACTIONS

Because of the risk of thrombocytopenia, caution should be used when using antiplatelet drugs (including nonprescription products that affect platelets) or anticoagulants concomitantly with TEGSEDI. 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.

Please see full Prescribing Information, including boxed WARNING, at TEGSEDIhcp.com.

ABOUT HEREDITARY TRANSTHYRETIN (hATTR) AMYLOIDOSIS

Hereditary ATTR amyloidosis is a severe, progressive, and life-threatening disease caused by the abnormal formation of the TTR protein and aggregation of TTR amyloid deposits in various tissues and organs throughout the body, including in peripheral nerves, the heart and intestinal tract. The progressive accumulation of TTR amyloid deposits in these organs often leads to intractable peripheral sensorimotor neuropathy, autonomic neuropathy, and/or cardiomyopathy, as well as other disease manifestations. Hereditary ATTR amyloidosis causes significant morbidity and progressive decline in quality of life, severely impacting activities of daily living. The disease often progresses rapidly and can lead to premature death. The median survival is 4.7 years following diagnosis. Additional information on hereditary ATTR amyloidosis, including a full list of organizations supporting the hATTR amyloidosis community worldwide, is available at www.hattrchangethecourse.com or by visiting www.hATTRGuide.com.

ABOUT AKCEA THERAPEUTICS, INC.

Akcea Therapeutics, Inc., a majority-owned affiliate of Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), is a biopharmaceutical company focused on developing and commercializing medicines to treat patients with serious and rare diseases. Akcea is commercializing TEGSEDI[®] (inotersen) and WAYLIVRA[®] (volanesorsen), as well as advancing a mature pipeline of novel medicines, including AKCEA-APO(a)-L_{RX}, vupanorsen (AKCEA-ANGPTL3-L_{RX}), AKCEA-APOCIII-L_{RX}, and AKCEA-TTR-L_{RX}, with the potential to treat multiple diseases. All six medicines were discovered by Ionis, a leader in antisense therapeutics, and are based on Ionis' proprietary antisense technology. TEGSEDI is approved in the U.S., E.U., Canada and Brazil. WAYLIVRA is approved in the E.U. and is currently in Phase 3 clinical development for the treatment of people with familial partial lipodystrophy, or FPL. Akcea is headquartered in Boston, Massachusetts, and is building the infrastructure to commercialize its medicines globally. Additional information about Akcea is available at www.akceatx.com and you can follow the Company on

Twitter at @akceatx.

FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding the business of Akcea Therapeutics, Inc. Any statement describing Akcea's goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of Akcea's medicines in development is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Akcea's forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Akcea's forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Akcea. In particular, we caution you that our forward-looking statements are subject to the ongoing and developing circumstances related to the COVID-19 pandemic, which may have a material adverse effect on our business, operations and future financial results. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Akcea's programs are described in additional detail in Akcea's quarterly reports on Form 10-Q and annual reports on Form 10-K, which are on file with the SEC. Copies of these and other documents are available from the company.

In this press release, unless the context requires otherwise, "Ionis", "Akcea," "Company," "Companies" "we," "our," and "us" refers to Ionis Pharmaceuticals and/or Akcea Therapeutics.

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