IONIS™ InBrief
6 April 2021

Ionis expands distribution agreement with Sobi to include TEGSEDI® in North America

Expanded agreement enables Ionis to focus its commercial efforts on high priority programs within its wholly owned pipeline, while ensuring continued access to TEGSEDI® for patients

Ionis' subsidiary Akcea has entered into a distribution agreement with Swedish Orphan Biovitrum AB (Sobi), an international biopharmaceutical company that focuses on rare diseases, to include the distribution of TEGSEDI® (inotersen) in North America (the "Expanded Agreement"). This follows the decision to commercialize TEGSEDI and WAYLIVRA® (volanesorsen) in Europe through a distribution agreement with Sobi.

Under the terms of the Expanded Agreement, Akcea retains the marketing authorization ("MAH") for TEGSEDI in North America (United States and Canada). Additionally, the company will continue to supply commercial product to Sobi, manage regulatory and manufacturing processes, relationships with key opinion leaders, and continue to lead the TEGSEDI global commercial strategy. Ionis is confident in Sobi's ability to ensure continued access of TEGSEDI for patients who depend on this important, transformative treatment.

KEY TAKEAWAY

This is an important step for Ionis to achieve its long-term vision and strategic goals. This agreement allows Ionis to focus its commercial efforts on high priority programs within its wholly owned pipeline, including its next generation LICA program IONIS-TTR-L_{Rx} (AKCEA-TTR-L_{Rx}).

> **"We are confident that this is the right course of action to deliver transformative medicines to patients in need, while enhancing value for Ionis shareholders. The actions taken today and over the last several months create a stronger organization better positioned to achieve our mission to transform the lives of millions of patients around the world by pioneering new markets and changing standards of care." Brett P. Monia, Ph.D., CEO**

Ionis expects to realize up to $50 million in annual cost savings beginning in 2022 as a result of the Expanded Agreement. In connection with this, the Company expects to incur restructuring charges of approximately $11 to $14 million principally in the quarter ending June 30, 2021.

ABOUT TEGSEDI® (INOTERSEN)

For important safety information, please go to next page.

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 x 109 /L
- Prior to starting TEGSEDI, obtain a platelet count. During treatment, monitor platelet counts weekly if values are 75 x 109 /L or greater, and more frequently if values are less than 75 x 109 /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 x 109 /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 x 109 /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 x 109 /L occurred in 25% of TEGSEDI-treated patients compared with 2% of patients on placebo. Platelet counts below 75 x 109 /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 x 109 /L. Follow recommended monitoring and treatment recommendations for platelet count.

Symptoms of thrombocytopenia can include unusual or prolonged bleeding (e.g., 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 (e.g., 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 (e.g., 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.