PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTEGSEDI™

inotersen injection

Solution; 284 mg inotersen / 1.5 mL per syringe [189 mg inotersen / mL (as inotersen sodium)]

Other nervous system drugs

Manufacturer:
Akcea Therapeutics, Inc.
22 Boston Wharf Rd
9th Floor
Boston, MA 02210
United States

Imported by:
Progress Therapeutics Inc.
14-320 Harry Walker Parkway North
Newmarket, ON
L3Y 7B4

Distributed by:
Innomar Strategies Inc.
3470 Superior Court
Oakville, Ontario, L6L 0C4
Canada

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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions, Immune	03/2022

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TEGSEDI™ (inotersen solution for subcutaneous injection) is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Evidence from the pivotal clinical study suggests that use in the geriatric population is not associated with major differences in safety or efficacy. Caution should

be used in these patients especially in regards to thrombocytopenia.

2 CONTRAINDICATIONS

TEGSEDI is contraindicated in patients who:

- Are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see *DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING*;
- Have a platelet count below 100 x 10^9/L before the start of treatment;
- With urine protein to creatinine ratio UPCR ≥ 113 mg/mmol (1 g/g) before the start of treatment;
- With an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73m^2 before the start of treatment;
- With severe liver impairment before the start of treatment

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Thrombocytopenia

TEGSEDI is associated with reductions in platelet count, which may result in thrombocytopenia (see ADVERSE REACTIONS). Platelet count should be monitored every 2 weeks during treatment with TEGSEDI and for 8 weeks following discontinuation of treatment.

Recommendations for adjustments to monitoring frequency and TEGSEDI dosing are specified in Table 1 (see Recommended Dose and Dosage Adjustment).

Patients should be instructed to report to their physician immediately if they experience any signs of unusual or prolonged bleeding (e.g. petechia, spontaneous bruising, subconjunctival bleeding, nosebleeds), neck stiffness or atypical severe headache.

Special caution should be used in elderly patients (who may be at greater risk of bleeding), in patients taking anithrombotic medicinal products, antiplatelet medicinal products, or medicinal products that may lower platelet count (see DRUG INTERACTIONS), and in patients with prior history of major bleeding events.

Glomerulonephritis

Glomerulonephritis has occurred in patients treated with TEGSEDI. Careful monitoring of UPCR and eGFR is important during treatment with TEGSEDI (see WARNINGS AND PRECAUTIONS – *Renal* and *Monitoring and Laboratory Tests*).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The following factors should be considered when dosing TEGSEDI:

- TEGSEDI is associated with reductions in platelet count, which may result in thrombocytopenia [see *Warnings and Precautions – Hematologic*]. Therefore,
    - Platelet count should be measured prior to treatment with TEGSEDI and as directed following treatment initiation (see *Recommended Dose and Dosage Adjustment* and *Warnings and Precautions - Monitoring and Laboratory Tests*).
    - TEGSEDI should not be initiated in patients with platelet count < 100 x 10^9/L.
    - Platelet count tests should be monitored regularly (see *Recommended Dose and Dosage Adjustment*).
    - Dosing should be adjusted according to laboratory values (see *Recommended Dose and Dosage Adjustment)*.
- Glomerulonephritis has occurred in patients treated with TEGSEDI. Therefore,
    - Estimated glomerular filtration rate (eGFR) and urine protein to creatinine ratio (UPCR) should be measured prior to treatment with TEGSEDI and as directed following treatment initiation (see WARNINGS AND PRECAUTIONS - *Monitoring and Laboratory Tests*).
    - TEGSEDI should not be initiated in patients with urine protein to creatinine ratio UPCR ≥ 113 mg/mmol (1 g/g) or an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73m2.

- Renal function tests should be monitored regularly [see WARNINGS AND PRECAUTIONS - *Monitoring and Laboratory Tests*].

- Plasma vitamin A (retinol levels) below the lower limit of normal (LLN) should be corrected and any ocular symptoms or signs of vitamin A deficiency should have resolved prior to initiation of TEGSEDI.

4.2 Recommended Dose and Dosage Adjustment

Treatment should be initiated by and remain under the supervision of a physician knowledgeable in the treatment of patients with hereditary transthyretin amyloidosis.

The recommended dose of TEGSEDI is 284 mg inotersen (300 mg inotersen sodium) injected subcutaneously once-weekly by a single-dose, prefilled syringe with a Safety Syringe Device (SSD).

For consistency of dosing, patients should be instructed to give the injection on the same day every week.

Patients receiving TEGSEDI should take oral supplementation of the recommended daily allowance (RDA) of vitamin A (approximately 3000 IU vitamin A per day). Vitamin A supplementation should be continued throughout treatment (see WARNINGS AND PRECAUTIONS – *Ophthalmologic*).

Reduced Platelet Count:

Dose adjustment in case of reduction in platelet count

TEGSEDI is associated with reductions in platelet count, which may result in thrombocytopenia. Dosing should be adjusted according to laboratory values as follows:

Table 1 TEGSEDI Monitoring and Treatment Recommendations for Platelet Count

Platelet Count (x 10^9/L)	Monitoring Frequency	Dosing
> 100	Every 2 weeks	Weekly dosing should be continued.
≥ 75 to < 100*	Every week	Dosing frequency should be reduced to 284 mg every 2 weeks. Weekly dosing may be resumed once platelet values >100.
< 75*	Twice weekly until 3 successive values above 75 x10^9/L then weekly monitoring.	Dosing should be paused until 3 successive values > 100. On reinitiation of treatment dose frequency should be reduced to 284 mg every 2 weeks.
< 50‡†	Twice weekly until 3 successive values above 75 then weekly monitoring. Consider more frequent monitoring if additional risk factors for bleeding are present.	Dosing should be paused until 3 successive values > 100. On reinitiation of treatment dose frequency should be reduced to 284 mg every 2 weeks. Consider corticosteroids if additional risk factors for bleeding are present.
< 25†	Daily until 2 successive values above 25. Then monitor twice weekly until 3 successive values above 75. Then weekly monitoring until stable.	Treatment should be discontinued. Corticosteroids recommended.

* If the subsequent test confirms the initial test result, then monitoring frequency and dosing should be adjusted as recommended in the table.

‡ Additional risk factors for bleeding include age > 60 years, receiving anticoagulant or anti-platelet medicinal products, and /or prior history of major bleeding events

† It is strongly recommended that, unless corticosteroids are contraindicated, the patient receives glucocorticoid therapy to reverse the platelet decline. Patients who discontinue therapy with TEGSEDI due to platelet counts below 25 x 10^9/L should not reinitiate therapy.

Renal Impairment: Since TEGSEDI is highly protein bound and is minimally cleared by the kidneys, no dose adjustment is required for patients with mild or moderate renal impairment. No data are available in patients with severe renal impairment.

Glomerulonephritis has occurred in patients treated with TEGSEDI.

Hepatic Impairment: TEGSEDI has not been evaluated in patients with known hepatic impairment or in patients with prior liver transplants. TEGSEDI is not metabolized by cytochrome P450 enzymes in the liver [see Pharmacokinetics *Metabolism*].

TEGSEDI is contraindicated in patients with severe hepatic impairment. Liver enzymes should be monitored prior to dosing and every four months, after treatment initiation. In patients with a history of liver transplant, monitor ALT, AST, and total bilirubin monthly. Treatment with TEGSEDI should be discontinued in patients with prior liver transplant who develop signs of transplant rejection *[see WARNINGS AND PRECAUTIONS Hepatic*].

Pediatric Population: Health Canada has not authorized an indication for pediatric use. [See INDICATIONS *Pediatrics*]

Geriatric Population: No dose adjustment is required for patients aged 65 years and over [see

WARNINGS AND PRECAUTIONS *Special Populations, Geriatrics*]

4.3 Administration

TEGSEDI should be administered as follows:

- TEGSEDI is intended for subcutaneous injection only.
- The first injection administered by the patient or caregiver should be performed under the guidance of an appropriately qualified health care professional. Patients and/or caregivers should be trained in the subcutaneous administration of TEGSEDI in accordance with the Instructions for Use [see *PATIENT MEDICATION INFORMATION*].
- Sites for injection include the abdomen, upper thigh region, or outer area of the upper arm. It is important to rotate sites for injection.
    - If injected in the upper arm, the injection should be administered by another person.
    - Injection should be avoided at the waistline and other sites where pressure or rubbing from clothing may occur.
    - TEGSEDI should not be injected into areas of skin disease or injury.
    - Tattoos and scars should also be avoided.
- TEGSEDI prefilled syringe should be allowed to reach room temperature prior to injection.
    - Remove from refrigerated storage (2 °C to 8 °C) at least 30 minutes prior to use.
    - Other warming methods should not be used.
- Use each prefilled syringe only once.

TEGSEDI should be inspected visually prior to administration. The solution should be clear and colorless to pale yellow. If the solution is cloudy or contains visible particulate matter, the contents must not be injected and the product should be returned to the pharmacy. TEGSEDI must not be injected if the expiration date on the carton has passed [see *STORAGE, STABILITY AND DISPOSAL* and *SPECIAL HANDLING INSTRUCTIONS*].

4.4 Reconstitution

TEGSEDI is supplied in a single-dose, prefilled syringe with an SSD, and therefore does not require reconstitution.

4.5 Missed Dose

If a dose is missed, patients should be instructed to take the missed dose as soon as possible, unless the next scheduled dose is within 2 days. In this case, the patient should be directed to skip the missed dose and take the next scheduled dose on the scheduled day.

5 OVERDOSAGE

During the premarketing evaluations of TEGSEDI, there were no reports of overdose.

In the event of an overdose, supportive medical care should be provided including consulting with a healthcare professional and close observation of the clinical status of the patient.

Platelet and renal function tests should be monitored regularly.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous Injection	Single dose prefilled syringe containing solution of 284 mg inotersen (300 mg inotersen sodium)/ 1.5 mL	Hydrochloric acid; Sodium hydroxide; and Water for injection

TEGSEDI is available as a sterile, clear, preservative-free, colourless to pale yellow solution for injection in a single-dose glass prefilled syringe containing 1.5 mL of solution (284 mg dose) with a Safety Syringe Device (SSD). TEGSEDI is available in cartons containing 4 prefilled syringes. Single use, discard unused portion.

7 WARNINGS AND PRECAUTIONS

Driving and Operating Machinery

TEGSEDI has not been shown to influence the ability to drive and use machines.

Hematologic

TEGSEDI is associated with reductions in platelet count, which may result in thrombocytopenia [See ADVERSE REACTIONS].

Careful monitoring for thrombocytopenia is important during treatment with TEGSEDI and recommended monitoring and treatment recommendations for platelet count found in Table 1 should be followed [see Recommended Dose and Dosage Adjustment]. Platelet counts should be verified prior to initiation of treatment, monitored during treatment every two weeks or more if needed (see Table 1), and continued for 8 weeks after discontinuation.

TEGSEDI should be used with special caution in patients treated with anti-thrombotic agents, antiplatelet agents, medications that may lower platelet count, in patients with a history of severe bleeding, or in the elderly, who may be at greater risk to bleeding.

Patients should be instructed to contact their physician immediately if they experience any signs of unusual or prolonged bleeding (e.g., petechia, spontaneous bruising, subconjunctival bleeding, nosebleeds, etc.), neck stiffness or atypical severe headache.

Hepatic

The liver is a site of accumulation of antisense oligonucleotides. 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 to 3% of patients on placebo; 3% of TEGSEDI-treated patients had an ALT at least 8 times the ULN, compared to no patient on placebo. One clinical study patient experienced an increased ALT more than 30 times the ULN. After a course of corticosteroids and discontinuation of TEGSEDI, the patient's ALT returned to normal levels. Some patients had resolution of the liver laboratory abnormalities with continued use of TEGSEDI.

In clinical studies, demonstrated or possible cases of immune-mediated biliary disease occurred in TEGSEDI-treated patients. There was a single case of autoimmune hepatitis with primary biliary cirrhosis in a patient with a family history of primary biliary cirrhosis, as well as a single case of biliary obstruction of unclear etiology.

Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin at baseline and every four months during treatment with TEGSEDI. If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), 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.

Immune

- **Hypersensitivity Reactions/Antibody Formation**

TEGSEDI can cause hypersensitivity reactions. In clinical studies, TEGSEDI-treated patients stopped treatment because of a hypersensitivity reaction. Antibodies to TEGSEDI were present when the reactions occurred. These reactions generally occurred within 2 hours of administration of TEGSEDI and included headache, chest pain, hypertension, chills, flushing, dysphagia, palmar erythema, eosinophilia, involuntary choreaform movements, arthralgia, myalgia, and flu-like symptoms. If a hypersensitivity reaction occurs, discontinue administration of TEGSEDI, and initiate appropriate therapy. Do not use in patients who have a history of hypersensitivity reaction to TEGSEDI.

- **Immunogenicity**

In the pivotal Phase 2/3 study, 30.4% of patients treated with TEGSEDI tested positive for anti-drug antibodies following 15 months of treatment. No effect on the pharmacokinetic properties (C_{max}, AUC or half-life) and efficacy of TEGSEDI was observed in the presence of anti-drug antibodies, but patients with anti-drug antibodies had more reactions at the injection site.

Monitoring and Laboratory Tests

Hematology**:** Platelet count should be monitored every 2 weeks during treatment with TEGSEDI, and dosage adjustments made as appropriate [see *Recommended Dose and Dosage Adjustment*].

Glomerulonephritis**:** UPCR and eGFR should be monitored every 3 months or more frequently, as clinically indicated, based on history of chronic kidney disease and/or renal amyloidosis. UPCR and eGFR should be monitored for 8 weeks following discontinuation of treatment. Patients with UPCR more than or equal to twice the upper limit of normal, or eGFR < 60 ml/min,

which is confirmed on repeat testing and in the absence of an alternative explanation, should be monitored every 4 weeks.

In the case of a decrease in eGFR > 30%, in the absence of an alternative explanation, pausing of TEGSEDI dosing should be considered pending further evaluation of the cause.

In the case of UPCR ≥ 2 g/g (226 mg/mmol), which is confirmed on repeat testing, dosing of TEGSEDI should be paused while further evaluation for acute glomerulonephritis is performed. TEGSEDI should permanently be discontinued if acute glomerulonephritis is confirmed. If glomerulonephritis is excluded, dosing may be resumed if clinically indicated and following improvement of renal function.

Early initiation of immunosuppressive therapy should be considered if a diagnosis of glomerulonephritis is confirmed.

Caution should be used with nephrotoxic medicinal products and other medicinal products that may impair renal function

Liver function: Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin at baseline and every four months during treatment with TEGSEDI. In patients with a history of liver transplant, monitor ALT, AST, and total bilirubin monthly.

Ophthalmologic

Vitamin A

Patients receiving TEGSEDI should take oral supplementation of the recommended daily allowance (RDA) of vitamin A (approximately 3000 IU vitamin A per day) in order to reduce the potential risk of ocular toxicity due to vitamin A deficiency. Vitamin A supplementation should be continued throughout treatment. Referral for ophthalmological assessment is recommended if patients develop ocular symptoms consistent with vitamin A deficiency.

Based on the mechanism of action of TEGSEDI it is expected that plasma retinol levels will be below LLN in patients treated with TEGSEDI. Additional vitamin A supplementation above RDA should not be given to attempt to correct this.

Renal

Glomerulonephritis has occurred in patients treated with TEGSEDI. In the Phase 3 trial, NEURO-TTR, glomerulonephritis occurred in three (3%) subjects treated with TEGSEDI and no patients treated with placebo. Renal function decline without glomerulonephritis was also reported. [See ADVERSE REACTIONS].

Careful monitoring of UPCR and eGFR is important during treatment with TEGSEDI. Follow recommended monitoring and treatment recommendations for renal parameters [see WARNINGS AND PRECAUTIONS *Monitoring and Laboratory Tests*].

Sexual Health

Reproduction

There are no published clinical data available on the effects of the use of TEGSEDI on the reproductive potential in females or males. TEGSEDI had no effect on the reproductive organs, mating, or pregnancy in animal studies.

Fertility

There is no information available on the effects of TEGSEDI on human fertility. Animal studies have shown no observable effects on male or female fertility.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled clinical studies with TEGSEDI in pregnant women. Due to the potential teratogenic risk arising from unbalanced vitamin A levels, TEGSEDI should only be used during pregnancy if the potential benefits justify the potential risk to the fetus.

Vitamin A levels during early pregnancy, both too high and too low, can impact fetal development. If a woman intends to get pregnant, both TEGSEDI treatment and vitamin A supplementation should be interrupted.

Due to the effect of TEGSEDI on vitamin A levels, there is a potential for impact on pregnancy. It is recommended that treatment should not be initiated in pregnant women and interrupted if pregnancy occurs. Women of child bearing age should use contraception during treatment.

7.1.2 Breast-feeding

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. 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.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of TEGSEDI included 69 patients (45%) aged 65 and over. No differences in safety, pharmacokinetics, or effectiveness were observed between these patients and younger patients.

8 ADVERSE REACTIONS

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

8.1 Adverse Reaction Overview

A total of 112 adult patients with polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR) received TEGSEDI in NEURO-TTR Study and 60 patients received placebo. The mean age of the study patients was 59 years (27 to 81 years of age). Of the TEGSEDI-treated patients, 68.8% were male and 93.8% were Caucasian, with a mean exposure of 385 days, and median exposure of 449 days (mean 55.6 doses, median 66 doses). Baseline disease characteristics were largely similar in the TEGSEDI-treated patients and placebo-control patients. Sixty-seven percent of patients were in Stage 1 of the

disease at baseline, with 33% being in Stage 2. Fifty-two percent of patients had Val30Met mutations in the TTR gene, with the remaining 48% comprised of 26 different other point mutations.

8.2 Serious Adverse Drug Reactions

Serious adverse reactions were more frequent in TEGSEDI-treated patients (32%) than in patients on placebo (22%). A >5% difference between treatment groups was observed in the incidence of serious TEAEs in the SOCs of Metabolism and Nutrition Disorders and Renal and Urinary Disorders.

Five patients died during the study and all received TEGSEDI treatment. Four of the deaths were consistent with progression of disease or a complication of the underlying disease. One fatal event (intracranial hemorrhage) occurred in association with Grade 4 thrombocytopenia with a platelet count of ~10 x 10^9/L at the time of hospital admission.

Three TEGSEDI-treated patients (3%) had sudden severe thrombocytopenia (platelet count below 25 x 10^9/L), which can have potentially fatal bleeding complications. Glomerulonephritis occurred in three (3%) TEGSEDI-treated patients (vs. no patient on placebo). (see WARNINGS AND PRECAUTIONS).

8.3 Most Frequent Adverse Drug Reactions

The most common adverse reactions that occurred in at least 20% of TEGSEDI-treated patients and that occurred more frequently than on placebo were injection site erythema, nausea, fatigue, diarrhea, headache and injection site pain.

Table 3 below presents common adverse reactions that occurred in at least 5% of TEGSEDI-treated patients and that occurred more frequently than on placebo.

Table 3 Adverse Reactions Reported in At Least 2% TEGSEDI-Treated Patients and that Occurred More Frequently than Placebo Patients (NEURO-TTR)

	Placebo N=60		Tegsedi 300mg N=112	
SYSTEM ORGAN CLASS	**Subjects**	**%**	**Subjects**	**%**
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Thrombocytopenia	1	1.7	15	13.4
Anaemia	2	3.3	14	12.5
Eosinophilia	0	0	3	2.7
CARDIAC DISORDERS				
Atrial fibrillation	1	1.7	6	5.4
Cardiac failure congestive	2	3.3	4	3.6
EAR AND LABYRINTH DISORDERS				
Vertigo	0	0	4	3.6
ENDOCRINE DISORDERS				
Hypothyroidism	1	1.7	3	2.7
EYE DISORDERS				
Cataract	1	1.7	5	4.5
Ocular hyperaemia	0	0	3	2.7
Vitreous floaters	0	0	3	2.7
GASTROINTESTINAL DISORDERS				
Nausea	7	11.7	35	31.3
Diarrhoea	12	20	26	23.2
Vomiting	3	5	17	15.2
Constipation	5	8.3	14	12.5
Dry mouth	1	1.7	6	5.4
Abdominal distension	1	1.7	3	2.7
Gastrooesophageal reflux disease	1	1.7	3	2.7
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Injection site erythema	0	0	35	31.3
Fatigue	12	20	28	25
Injection site pain	4	6.7	23	20.5
Oedema peripheral	5	8.3	21	18.8
Pyrexia	5	8.3	21	18.8
Chills	2	3.3	20	17.9
Injection site pruritus	0	0	13	11.6
Influenza like illness	2	3.3	9	8
Injection site bruising	2	3.3	8	7.1
Peripheral swelling	0	0	7	6.3
Injection site reaction	0	0	6	5.4
Injection site swelling	0	0	6	5.4
Injection site discolouration	0	0	5	4.5
Injection site rash	0	0	5	4.5
Injection site haemorrhage	1	1.7	4	3.6
Injection site induration	0	0	4	3.6
Chest pain	0	0	3	2.7
Injection site haematoma	1	1.7	3	2.7
Injection site inflammation	0	0	3	2.7

SYSTEM ORGAN CLASS	Placebo N=60 Subjects	%	Tegsedi 300mg N=112 Subjects	%
INVESTIGATIONS				
Platelet count decreased	0	0	11	9.8
Glomerular filtration rate decreased	2	3.3	6	5.4
Aspartate aminotransferase increased	2	3.3	5	4.5
Blood creatine phosphokinase increased	2	3.3	5	4.5
Blood urea increased	0	0	3	2.7
Eosinophil count increased	0	0	3	2.7
Transaminases increased	0	0	3	2.7
METABOLISM AND NUTRITION DISORDERS				
Decreased appetite	0	0	11	9.8
Dehydration	1	1.7	4	3.6
Vitamin D deficiency	0	0	3	2.7
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Myalgia	6	10	17	15.2
Arthralgia	5	8.3	13	11.6
Back pain	5	8.3	10	8.9
Muscle spasms	4	6.7	10	8.9
Musculoskeletal pain	1	1.7	5	4.5
Musculoskeletal stiffness	1	1.7	4	3.6
NERVOUS SYSTEM DISORDERS				
Headache	7	11.7	25	22.3
Paraesthesia	2	3.3	10	8.9
Syncope	2	3.3	8	7.1
Presyncope		0	6	5.4
Migraine	2	3.3	5	4.5
Somnolence	2	3.3	4	3.6
Balance disorder	1	1.7	3	2.7
Loss of consciousness	0	0	3	2.7
PSYCHIATRIC DISORDERS				
Depression	2	3.3	7	6.3
RENAL AND URINARY DISORDERS				
Proteinuria	2	3.3	7	6.3
Acute kidney injury	0	0	3	2.7
Chronic kidney disease	0	0	3	2.7
Renal failure	0	0	3	2.7
Renal impairment	0	0	3	2.7
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Dyspnoea	2	3.3	10	8.9
Oropharyngeal pain	2	3.3	5	4.5
Pleural effusion	0	0	3	2.7
Productive cough	0	0	3	2.7

SYSTEM ORGAN CLASS	Placebo N=60 Subjects	%	Tegsedi 300mg N=112 Subjects	%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Erythema	2	3.3	5	4.5
Hyperhidrosis	1	1.7	4	3.6
Pruritus	1	1.7	4	3.6
Rash	1	1.7	4	3.6
Skin ulcer		0	4	3.6
Night sweats	1	1.7	3	2.7
Skin lesion	1	1.7	3	2.7
Urticaria	1	1.7	3	2.7
VASCULAR DISORDERS				
Orthostatic hypotension	0	0	7	6.3
Hypotension	2	3.3	6	5.4
Haematoma	1	1.7	4	3.6
Hypertension	0	0	4	3.6

8.3.1 Adverse Events Leading to Withdrawal or Discontinuations

Eight (8) patients treated with TEGSEDI and 1 patient treated with placebo withdrew from the study due to adverse events. The only TEAE leading to withdrawal from study observed in > 1 subject in the TEGSEDI group was cachexia, which is a common complication of hATTR-PN.

Sixteen (16) TEGSEDI-treated patients and 2 placebo treated patients permanently discontinued treatment due to adverse event (including case of stopping rule met). Three TEGSEDI-treated patients discontinued due to thrombocytopenia and two patients discontinued due to glomerulonephritis (one of which was initially reported as acute kidney injury). One additional patient developed glomerulonephritis at the end of treatment period and did not enter the open label extension study.

8.3.2 Adverse Events Leading to Dose Reductions or Pauses

The dose of TEGSEDI was reduced in 3 patients due to adverse events. Twenty-seven (27) TEGSEDI-treated patients and 3 placebo treated patients had interruptions or delays in dosing due to adverse events. The most common reasons for dose reductions or interruptions were platelet or kidney related issues.

8.3.3 Concomitant Medication to Treat an Adverse Drug Reaction Symptom

Common adverse drug reactions that required treatment in the TEGSEDI treated group with another medication included in the Gastrointestinal Disorders SOC, nausea 16 patients (14%) and vomiting 7 patients (6%). In the General Disorders and Administration Site Conditions, 14 patients (13%) who reported pyrexia required a concomitant medication to treat the reported symptomatology.

8.4 Adverse Reactions of Special Interest

8.4.1 Thrombocytopenia

TEGSEDI is associated with reductions in platelet count, which may result in thrombocytopenia. In the Phase 2/3, NEURO-TTR trial, platelet count reductions to below normal (140 x 10^9/L) were observed in 54% of patients treated with TEGSEDI and 13% of placebo patients; reductions to below 100 x 10^9/L were observed in 23% of patients treated with TEGSEDI and 2% of the patients receiving placebo; confirmed platelet counts of < 75 x 10^9/L were observed in 10.7% of TEGSEDI-treated patients. Three (3%) patients developed platelet counts < 25 x 10^9/L; one of these patients experienced a fatal intracranial haemorrhage. Patients should be monitored for thrombocytopenia during treatment with TEGSEDI (see WARNINGS AND PRECAUTIONS).

8.4.2 Glomerulonephritis / Renal Function Decline

Three (3) patients developed glomerulonephritis in the course of the NEURO-TTR study. Severe and serious renal impairment were more common in TEGSEDI-treated subjects compared to placebo (4.5% vs. 1.7% and 5.4% vs. 0%) including glomerulonephritis, tubulointerstitial nephritis, acute kidney injury, renal failure and renal impairment. Patients should be monitored for signs of increased proteinuria and reduction in eGFR during treatment with inotersen (see WARNINGS AND PRECAUTIONS).

8.4.3 Injection Site Adverse Events

Adverse events at the injection site were commonly reported in TEGSEDI-treated patients. These reactions included injection site pain, erythema, pruritus, swelling, rash, induration, bruising and haemorrhage. These reactions were generally self-limiting and manageable.

8.5 Immunogenicity

See WARNINGS AND PRECAUTIONS - *Immunogenicity*

8.6 Clinical Trial Adverse Reactions (Pediatrics)

TEGSEDI has not been studied in the pediatric population, and there are therefore no clinical trial adverse reactions to report.

8.7 Post-market Adverse Reactions

The following adverse reaction has been identified during the post-approval use of inotersen:

- Hypersensitivity. See Warnings and Precautions – Immune - Hypersensitivity Reactions.

9 DRUG INTERACTIONS

9.1 Overview

TEGSEDI is not a substrate of cytochrome P450 (CYP450) and did not induce or inhibit CYP450 in vitro. TEGSEDI was not a substrate or inhibitor of major transporters. These studies

indicated a lack of interaction potential. No formal clinical drug-drug interaction studies have been conducted.

The effect of commonly used concomitant medications, which included diuretics, anti-thrombotics, and non-steroid anti-inflammatory drug (NSAID) analgesics, was evaluated by population PK analysis. None of the evaluated concomitant medications showed a clinically significant effect on the clearance of TEGSEDI.

Clinically relevant pharmacokinetic interactions are not expected for TEGSEDI.

Caution should be used with antithrombotic medicinal products, antiplatelet medicinal products, and medicinal products that may lower platelet count, for example acetylsalicylic acid, clopidogrel, warfarin, heparin, low-molecular weight heparins, Factor Xa inhibitors such as rivaroxaban and apixaban, and thrombin inhibitors such as dabigatran [see WARNINGS AND PRECAUTIONS– *Hematologic*].

Caution should be exercised with concomitant use of nephrotoxic medicinal products and other medicines that may impair renal function, such as sulfonamides, aldosterone antagonists, anilides, natural opium alkaloids and other opioids [see WARNINGS AND PRECAUTIONS – *Renal*].

9.2 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.3 Drug-Food Interactions

Interactions with food, drink, or alcohol are not expected with TEGSEDI.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Inotersen is a 2′-O-(2-methoxyethyl) (2′-MOE) phosphorothioate antisense oligonucleotide (ASO) complementary to the molecular target transthyretin (TTR) messenger RNA (mRNA). Hereditary transthyretin amyloidosis (hATTR), is a rare autosomal dominant, progressive systemic disease caused by mutations in the gene that codes for the protein transthyretin (TTR). The mutations result in weakening of the bonds of the normal tetrameric structure, which disaggregate into monomers that are prone to misfolding. These misfolded proteins, self-assemble into amyloid fibrils in various organs and tissues throughout the body including peripheral neurons, the gastrointestinal tract and the heart. The selective binding of TEGSEDI to the TTR mRNA causes the degradation of both mutant and wild type (normal) TTR mRNA. Degradation of TTR mRNA prevents the synthesis of TTR in the liver, resulting in significant

reductions in the levels of mutated and wild type TTR protein secreted by the liver into the circulation.

TTR is a carrier protein for retinol-binding protein 4 (RBP4) which is the principle carrier of vitamin A (retinol). Therefore, reduction in plasma TTR is expected to result in reduction of plasma retinol levels to lower limit of normal. TTR is also a carrier protein for thyroxine.

10.2 Pharmacodynamics

Effects of TEGSEDI on Transthyretin (TTR)

In the pivotal NEURO-TTR study, in the TEGSEDI treatment group, robust reduction in circulating TTR levels was observed throughout the 15-month treatment period, with mean percent changes from Baseline in serum TTR from Week 13 to Week 65 ranging from 68% to 74% (median range: 74.64% to 78.98%). In the placebo group, mean serum TTR concentration decreased by 8.50% at Week 3 and then remained fairly constant throughout the treatment period.

The relationship between the TTR concentration and disease progression is unknown. It is unclear what level of reduction of TTR protein produces benefits to polyneuropathy measurements. There was no correlation with the 300 mg dose between the absolute or relative change from baseline in serum transthyretin levels and the change from baseline scores for either of the two primary scales [modified Neuropathy Impairment Scale + 7 (mNIS+7) composite score, and Norfolk Quality of Life –Diabetic Neuropathy (QoL-DN)]. No other doses were included in the phase 2/3 NEURO-TTR study.

Cardiac Electrophysiology

A Thorough QT prolongation (TQT) study has not been conducted but electrocardiogram (ECG) monitoring was done in clinical trials. There is no evidence that treatment with TEGSEDI prolongs the QTc interval. Inotersen was negative in the human ether-related-a-go-go gene (hERG) assay.

10.3 Pharmacokinetics

Single- and multiple-dose pharmacokinetics (PK) of TEGSEDI were determined in healthy volunteers (range 50 to 400 mg weekly), with additional data from a small subset (n = 10) of patients with hATTR (300 mg weekly), and from a population pharmacokinetic (PK) analysis.

Absorption: Following subcutaneous (SC) administration, TEGSEDI is absorbed rapidly into systemic circulation in a dose-dependent fashion with the median time to maximum plasma concentrations (Cmax) of TEGSEDI of 2 to 4 hours.

Distribution: TEGSEDI is highly bound to human plasma proteins (>94%) and the fraction bound is independent of drug concentration. Mean plasma concentrations decreased by > 90% from the peak by 24 hours after SC injections. Based on population PK analysis, the apparent volume of distribution of TEGSEDI at steady-state is 293 L in patients with hATTR. The high volume of distribution suggests inotersen extensively distributes into tissues following SC administration. This is consistent with animal studies (mouse, rat and monkey), showing that TEGSEDI rapidly and extensively distributes to various tissues, with the highest concentrations

observed in the kidney followed by the liver, as well as mesenteric lymph nodes, bone marrow, thyroid, spleen, bone and pancreas. TEGSEDI does not readily cross the blood-brain barrier.

Metabolism/Biotransformation: As expected for an antisense oligonucleotide, in-vitro studies indicate that TEGSEDI is not a substrate for cytochrome CYP 450 metabolism, and clinical data indicate that it is metabolized slowly in tissues by endonucleases to form shorter inactive oligonucleotides that are the substrates for additional metabolism by exonucleases. Unchanged TEGSEDI is the predominant circulating component after four weeks of dosing in healthy subjects (approximately 74% of the total oligonucleotides detected in human plasma).

Elimination: The elimination of TEGSEDI involves both metabolism in tissues and excretion of primarily the chain-shortened metabolites in urine. Urinary recovery of the parent drug is limited to less than 1% within the 24 hours post dose consistent with minimal glomerular filtration due to being highly bound to plasma protein. Following subcutaneous administration, elimination half-life for TEGSEDI is approximately 1 month.

Special Populations and Conditions

Based on the population PK analysis, age, body weight, sex or race appears to have no clinically relevant effect on TEGSEDI exposure. Definitive assessments were limited due to low numbers.

Hepatic Insufficiency: The pharmacokinetics of TEGSEDI in patients with hepatic impairment has not been studied.

Renal Insufficiency: A population pharmacokinetic analysis suggests that mild and moderate renal impairment has no clinically relevant effect on the systemic exposure of TEGSEDI. No data are available in patients with severe renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

TEGSEDI is a clear, colorless to pale yellow solution supplied in a single-dose, prefilled syringe with a Safety Syringe Device (SSD). Each prefilled syringe of TEGSEDI is filled to deliver a 284 mg dose of inotersen.

Store under refrigeration at 2 °C to 8 °C in the original container and protect from exposure to direct light. Keep out of reach and sight of children.

Remove from refrigerated storage (2 °C to 8 °C) at least 30 minutes before use. TEGSEDI prefilled syringe should be allowed to reach room temperature (20 °C to 25 °C) prior to injection.

TEGSEDI may be stored unrefrigerated (2 °C to 30 °C) in the original container for up to 6 weeks; if not used within the 6 weeks, discard TEGSEDI.

12 SPECIAL HANDLING INSTRUCTIONS

Avoid exposure to temperatures above 30 °C.

PART II : SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

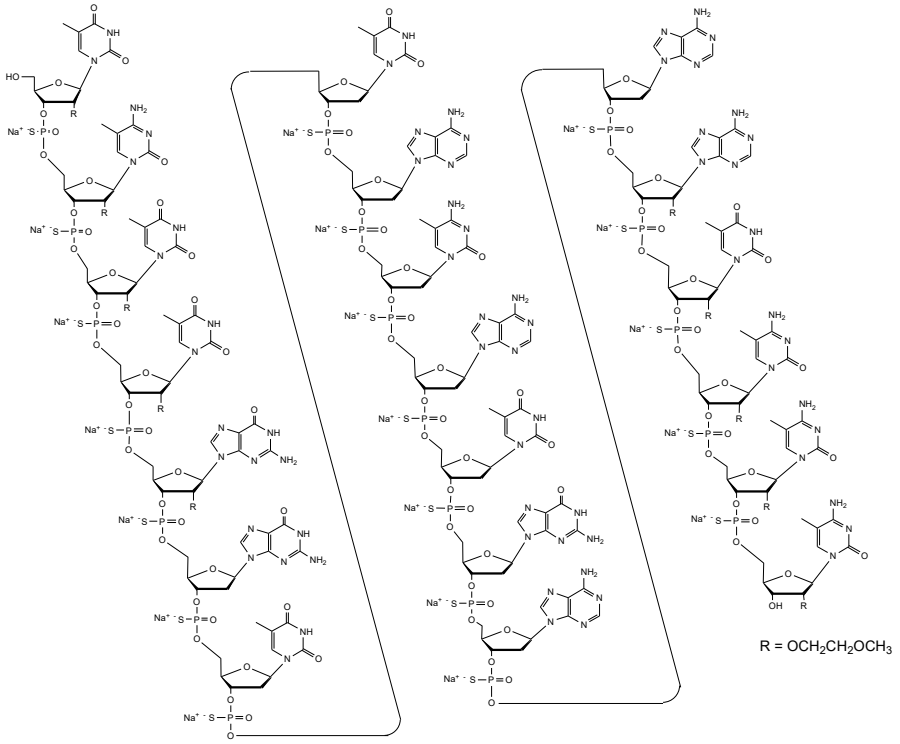
Drug Substance

Common name: inotersen

Chemical name: 2′-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thioguanylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thiothymidylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thiothymidylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thioadenylyl-(3′-*O*→5′-*O*)-2′-deoxy-5-methyl-*P*-thiocytidylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thioadenylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thiothymidylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thioguanylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thioadenylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thioadenylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-5-methylcytidine, nonadeca sodium salt.

Molecular formula and molecular mass: The molecular formula of inotersen sodium is $C_{230}H_{299}N_{69}O_{121}P_{19}S_{19}Na_{19}$ and the molecular weight is 7600.8 Da.

Structural formula:



Physicochemical properties:

Inotersen sodium comprises 20 nucleotides connected via 19 phosphorothioate linkages that are fully ionized as the sodium salt.

Inotersen sodium is a white to pale yellow solid. Inotersen sodium is freely soluble in water, methanol and in phosphate buffer (pH 7.5 and pH 8.5) and insoluble in acetonitrile.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Efficacy of TEGSEDI was demonstrated in a Phase 3 randomized, double-blind, placebo-controlled, multicenter clinical trial (NEURO-TTR trial) in patients with hATTR.

The NEURO-TTR study was a multicenter, placebo-controlled trial with 172 hereditary Transthyretin Amyloidosis with Polyneuropathy (hATTR-PN) patients treated. hATTR-PN patients can be divided into 3 diseases stages according to their ambulatory status: stage 1 need no assistance, stage 2 need assistance with one or two devices (e.g. canes), and stage 3 are wheelchair or bed bound. Only patients with Stage 1 or Stage 2 hATTR-PN and a neuropathy impairment score (NIS) ≥10 and ≤130 were evaluated. Patients were randomized 2:1 to receive either TEGSEDI or placebo. TEGSEDI (284 mg inotersen) was administered as a subcutaneous injection 3 times in the first week and then once weekly in Weeks 2 to 65. Sixty-two percent (62%) of patients also had TTR cardiomyopathy at baseline. Patients were randomized 2:1 to receive either TEGSEDI or placebo.

The primary efficacy endpoints were the change from baseline to Week 66 in the modified NIS+7 (mNIS+7) composite score and in the Norfolk Quality of Life (QoL)-Diabetic Neuropathy questionnaire total score. The mNIS +7 is a composite measure that consists of 2 components: the NIS composite score and the modified SUM7 Test (+7) composite score. The NIS component measures deficits in the strength of muscles innervated by the cranial nerves, muscle strength, reflexes, and sensation of the big toe and index finger. The modified +7 component of the mNIS+7 includes 4 elements: nerve conduction, heart rate to deep breathing (HRDB), touch-pressure sensation, and heat-pain (i.e., heat as pain) sensation testing. The total score ranges from 0 to 346.3 points, where an increasing score indicates worsening impairment. The Norfolk QoL-DN questionnaire is a patient-reported measure of the impact of neuropathy symptoms on quality of life. Both primary endpoints were also assessed at Week 35.

Baseline demographic and disease characteristics are shown in Table 4.

Table 4 Summary of patient demographics for clinical trials in hATTR

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age	Sex
NEURO-TTR	A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study	TEGSEDI (Inotersen 284 mg) or placebo; SC; 3 times in Week 1 followed by once weekly Weeks 2–65	172 (112 on TEGSEDI; 60 on placebo)	59.2 years	Male 68.6% Female 31.4%

14.2 Study Results

The changes from Baseline in both primary endpoints (mNIS+7 and Norfolk QoL-DN) demonstrated statistically significant benefit in favor of TEGSEDI treatment as early at Week 66 (Table 5).

Table 5 Primary Endpoint Analysis mNIS+7 and Norfolk QoL-DN

	mNIS+7		Norfolk-QOL-DN	
	Placebo (N=60)	TEGSEDI (N=112)	Placebo (N=60)	TEGSEDI (N=112)
Baseline				
n	60	112	59	111
Mean (SD)	74.75 (39.003)	79.16 (36.958)	48.68 (26.746)	48.22 (27.503)
Week 66 Change				
n	60	112	59	111
LSM (SE)	25.43 (3.225)	10.54 (2.397)	12.94 (2.840)	4.38 (2.175)
95% CI	19.11, 31.75	5.85, 15.24	7.38, 18.51	0.11, 8.64
Difference in LSM (Tegsedi – Placebo)		-14.89		-8.56
95% CI		-22.55, -7.22		-15.42, -1.71
P-value		<0.001		0.015

Patients were stratified for stage of disease (Stage 1 versus Stage 2), TTR mutation (V30M versus non-V30M) and previous treatment with either tafamidis or diflunisal (yes versus no). Results across these characteristics at Week 66 showed statistically significant benefit in all subgroups based on mNIS+7 composite score in all but one of these subgroups (CM-Echo Set) based on Norfolk QoL-DN total score. Furthermore, results across the components of mNIS+7 and domains of Norfolk QoL-DN composite scores were consistent with the primary endpoint analysis, showing benefit in motor, sensory and autonomic neuropathies. Results from secondary and exploratory endpoints failed to consistently show significant improvement of cardiomyopathy.

15 MICROBIOLOGY

TEGSEDI is not an antimicrobial product, and information and data regarding microbiology are therefore not applicable.

16 NON-CLINICAL TOXICOLOGY

16.1 Pharmacokinetics

After subcutaneous injection to mice, rats, and monkeys, plasma inotersen levels reached Cmax at 0.5 to 2 h and then rapidly declined in a multi exponential fashion characterized by an initial rapid distribution into tissues phase, followed by a slower elimination phase. The major tissues of distribution were the kidneys, liver, mesenteric lymph nodes, bone marrow, thyroid, spleen, bone and pancreas. Inotersen did not readily cross the blood-brain barrier. In embryo-fetal development studies, there was no measurable inotersen in fetal liver of rabbits and mice, indicating inotersen is not readily transported to the embryo or fetus. Since inotersen levels in mouse breast milk were less than 0.2% of maternal liver concentrations and bioavailability after oral administration is minimal, transfer of inotersen to nursing pups via maternal exposure is unlikely. Kidney generally contained the highest concentration of inotersen followed by the liver with steady state reached within 13 weeks. Elimination from the tissues, either as inotersen, or as a result of mainly nuclease-mediated metabolism was slow. Very little inotersen was present in the urine or feces. Once formed, the shortened oligonucleotide metabolites were rapidly eliminated mainly in urine and feces, with minimal amounts detected in plasma and tissues.

16.2 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a subcutaneous carcinogenicity study in rasH2 transgenic mice, inotersen was administered for 26 weeks at doses of 10, 30, and 80 mg/kg/week. There was no evidence of carcinogenicity for inotersen following 26 weeks of treatment in mice.

Subcutaneous administration of inotersen to Sprague-Dawley rats for up to 94 weeks at dose levels of 0.5, 2, and 6 mg/kg/week resulted in dose-dependent incidences of subcutaneous malignant pleomorphic fibrosarcoma and increased incidences of malignant fibrosarcoma of the monomorphic type in the injection sites or injection site regions (once weekly doses rotated between intrascapular and dorsal to tail areas) of both sexes at 2 and 6 mg/kg/week.

Inotersen did not exhibit genotoxic potential in a battery of studies, including the in vitro Bacterial Reverse Mutation (Ames) assay, an in vitro cytogenetics assay using Chinese Hamster Lung (CHL) cells, and an in vivo micronucleus assay in mice.

Transfer of antisense oligonucleotides, such as inotersen, across the placenta is restricted because of their size, molecular charge, water solubility, and high plasma protein binding. Thus, there was no detectable inotersen in fetal tissues in fetal mouse liver after subcutaneous dosing during the period of organogenesis. In reproductive and developmental toxicity studies in mice and rabbits, at doses (administered every second day) that exceeding the maximum recommended human equivalent dose, there were no effects on organogenesis. Lower fetal body weight at the highest dose tested in rabbits was attributed to reduced maternal food consumption and body weight.

A pre- and post-natal development study in pregnant/lactating female mice conducted to evaluate potential adverse effects of subcutaneous administration of inotersen from gestation day 6 through lactation day 20, development of the conceptus, and development of the offspring following exposure of the female from implantation through weaning showed concentrations of

inotersen in breast milk were very low compared to liver concentrations (at subcutaneous doses up to 80 mg/kg/week). Due to the poor oral bioavailability of inotersen it is considered unlikely that these low milk concentrations will result in systemic exposure from nursing.

Inotersen had no effect on fertility in mice at doses up to 87.5 mg/kg/week administered as subcutaneous injections of 25 m/kg every second day.

Since inotersen is not pharmacologically active in mice, the developmental consequences of TTR reduction were evaluated using a mouse-specific TTR analog. Approximately 40% reduction in TTR mRNA of maternal liver was produced with a 40 mg/kg dose. There were no developmental effects in mice associated with this level of TTR reduction. A rabbit-specific TTR inhibitor was not evaluated.

16.3 Animal Toxicology and/or Pharmacology

Decreased platelet count was observed in monkeys after approximately 13 weeks or longer of treatment with inotersen. The decreases were sufficiently severe in 2 males (platelet count $< 50 \times 10^9$/L), one at each of 10 and 20 mg/kg/week, as to cause bleeding or bruising. The inability to maintain platelet count with continued treatment lead to the cessation of dosing and euthanasia of both animals. Moderate decreases (platelet count $> 100 \times 10^9$/L) were observed at least once in the 4 other affected male and female monkeys ≥ 6 mg/kg/week. Platelet counts recovered after short-term dosing holidays; until the end of study for one low dose male with a moderate decrease, but only temporarily for the high dose male with a severe decrease. The effect was attributed to increased peripheral platelet consumption, since there was no evidence of bone marrow toxicity or thrombosis. Decreased platelet counts also occurred in mice and rats given inotersen; however, they were less severe and without clinical consequences.

Microscopic evidence of inotersen accumulation was evident as basophilic granules and vacuolation in renal tubular epithelial cells and tissue macrophages, often accompanied by hypertrophy, in multiple organs of mice, rats, and monkeys at virtually all dose levels tested. The principal organs affected were the kidneys and liver, which have the highest concentration of inotersen with lymph nodes and injection sites also consistently affected. These findings were generally not considered adverse, but evidence of renal toxicity was seen in monkeys (tubular epithelial degeneration/regeneration, erythrocytic tubular casts, multifocal mononuclear cell infiltration, fibroconnective tissue proliferation and hemorrhage correlating with hematuria and elevated protein/creatinine ratios) at the highest dose tested (40 mg/kg/week) and in rats (increased glomerular cellularity and matrix and proteinuria) at 15 and 40 mg/kg/week, with some evidence of hepatotoxicity also evident in rats at 15 and 40 mg/kg/week. Systemic exposure to inotersen, at the no effect doses was, 1.7 and 6.6 times that at the human dose for rats and monkeys respectively. Another common effect of inotersen was inflammatory changes in numerous organs in mice, rats and monkeys. This included mononuclear cell infiltrates and increases in lymphoid organ weights, associated with increases in plasma cytokines, chemokines and/or total serum IgG and IgM. In addition, reduced thymus weight due to lymphocyte depletion was observed in mice and rats and perivascular cell infiltration by lymphohistiocytic cells in multiple organs noted in monkeys.

Complement activation and increases in D-dimer concentration were observed at all subcutaneous inotersen dose levels in a 39-week study in monkeys.

Findings in rats given inotersen at 5, 15 and 40 mg/kg/week for 26 weeks included hypertrophy/hyperplasia of ovarian interstitial stromal cells and increased ovary weight, increased endometrial thickness due to expansion/edema of the stroma in the uterus, increases in hematopoietic cellularity and proliferation of vacuolated eosinophilic cells in the bone marrow and increased trabecular bone occurred in one or both sexes given inotersen at all dose levels. However, similar findings were not observed in mice and monkeys dosed for up to 26 and 39 weeks, respectively, and therefore the significance of these findings for patients is considered limited.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

TEGSEDI™
inotersen injection

Read this carefully before you start taking **TEGSEDI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TEGSEDI**.

SERIOUS WARNINGS AND PRECAUTIONS

Decreased platelet count (Thrombocytopenia):

TEGSEDI can lower the platelet count in your blood. Your doctor should monitor you every 2 weeks while you are taking TEGSEDI and for 8 weeks after you stop taking it.

This is especially important if you are:
- eldery (since you may be at a greater risk of bleeding), or
- taking medicines to prevent the formation of blood clots or platlets or those lower your platlet count.

If you experience or notice:
- unusual or prolonged bleeding (such as a rash of red spots on your skin, spontaneous bruising or bleeding in your eye)
- stiffness in your neck or
- an unusual severe headache

Call your doctor **right away**.

Glomerulonephritis / kidney problems

Some patients taking TEGSEDI have developed glomerulonephritis. This is a condition where your kidneys do not work properly. Your doctor will check how well your kidneys are working before you start TEGSEDI, regularly while you are taking TEGSEDI, and for 8 weeks after you stop taking it.

Symptoms of glomerulonephritis are:
- foaming urine
- pink or brown coloured urine
- blood in the urine, and
- passing less urine than usual

Some patients taking TEGSEDI have also developed a decline in how well their kidneys are working without having had glomerulonephritis.

Tell your doctor if you are taking any medicines that damage the kidneys or affect kidney function, for example sulfonamides, aldosterone antagonists, and some types of painkillers.

What is TEGSEDI used for?
TEGSEDI is used for treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR).

In hATTR, a change or mutation in the gene alters the structure of the TTR protein causing it to fold into an unusual shape or clump together and build up in the body. This buildup of TTR can stop the organs in your body from working properly.

How does TEGSEDI work?

TEGSEDI belongs to a group of medicines called anti-sense oligonucleotides (ASO). It helps to reduce the levels of TTR proteins in the body by preventing TTR production by the liver.

What are the ingredients in TEGSEDI?
Medicinal ingredients: inotersen (as inotersen sodium)
Non-medicinal ingredients: hydrochloric acid; sodium hydroxide and water for injection

TEGSEDI comes in the following dosage forms:
Sterile solution for subcutaneous use; 284mg Inotersen / 1.5ml per syringe

Do not use TEGSEDI if:
- You are allergic to inotersen or to any ingredient in the formulation
- Your blood platelet count is below 100 x 10^{9} per liter.
- Your kidney function test results are:
    - Protein to creatinine ratio (UPCR) ≥ 113 mg / mmol
    - Estimated glomerular filtration rate (eGFR) < 45 mL / min / 1.73 m^2
- Suffer from severe liver disease.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEGSEDI. Talk about any health conditions or problems you may have, including if:

- Your blood platelet count is low. Some symptoms of low platelet count are:
    - Easy or unexplained bruising
    - Prolonged bleeding from cuts
    - Blood in urine or stools
    - Bleeding from your gums and nose
    - Bleeding into the skin that appears as a rash of red spots
- You take blood thinners or medications that may lower the platelet count such as acetylsalicylic acid, warfarin
- You had severe bleeding in the past
- You are 65 years or older
- You had a liver transplant in the past
- You suffer from kidney damage
- You take any medication that may damage your kidney function, such as some pain killers (opioids)
- You are breast-feeding. It is not known if TEGSEDI can pass into breast milk.

Other warnings you should know about:

Low levels of Vitamin A:
If you experience symptoms of low vitamin A before starting TEGSEDI, your doctor will recommend you take a vitamin A supplement. Once your symptoms are gone, your doctor will start you on TEGSEDI.

TEGSEDI may decrease the levels of Vitamin A in your body and you may need to take a vitamin A supplement while on it. Your doctor will tell you the correct dose of vitamin A for you.

- Some symptoms of low vitamin A include:
  - dry eyes
  - poor vision
  - decreased night vision
  - hazy or cloudy vision

Pregnancy:
- **Talk to your doctor right away if** you are pregnant, think you may be pregnant or are planning to become pregnant. TEGSEDI may affect your levels of vitamin A and low or high levels of vitamin A can harm the baby.
- If you are of child bearing age, you should use contraceptive method while on this treatment

Risk of bleeding:
TEGSEDI may decrease the platelet count in your blood. Platelets are blood cells that help blood clot.

Laboratory Tests:
Your doctor will perform laboratory tests to assess the effects of TEGSEDI on your:

- **Kidneys:** blood and urine tests to measure your kidneys function, before starting TEGSEDI, every 4 weeks or more often is needed, and 8 weeks after stopping TEGSEDI.
- **Liver:** blood tests to measure your liver function, before starting TEGSEDI, and every 4 months after that.
- **Platelets count:** blood tests before starting the treatment with TEGSEDI, every two weeks or more often if needed, and continue 8 weeks after stopping TEGSEDI.

Allergic reactions:
TEGSEDI may cause serious allergic reactions. These allergic reactions often occur within 2 hours after injecting TEGSEDI. Get emergency help immediately if you have any symptoms of an allergic reaction including:
  - difficulty swallowing
  - chest pain or joint pain or muscle pain
  - high blood pressure
  - flu-like symptoms or chills or flushing
  - redness on the palms of your hands
  - tremor or jerking movements.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TEGSEDI:
Interactions with other drugs are not known.

How to give TEGSEDI:
- It is important to rotate injection sites.
- Choose a different spot each time you inject TEGSEDI.

If you are a caregiver:
- you can give the injection just below the skin of the lower part of the belly area, front of the thigh or upper arm

If you are the patient:
- Inject TEGSEDI just below the skin of the lower part of the belly area or the front of the thigh.

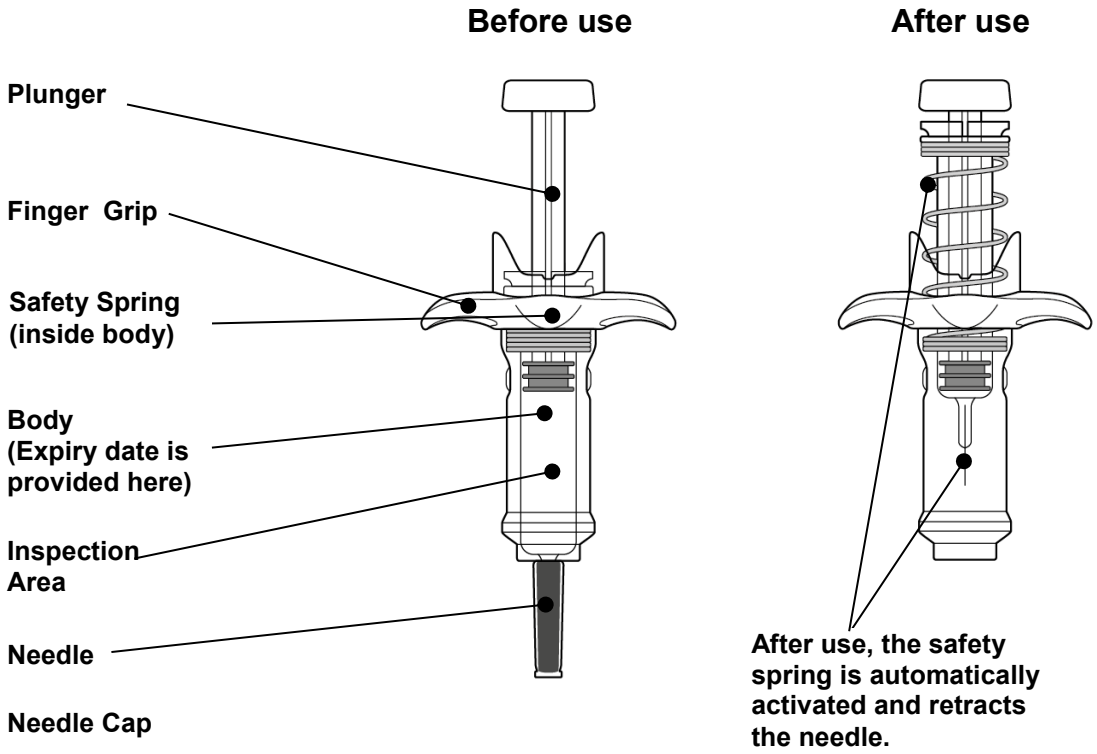
INSTRUCTIONS FOR USE

Before using TEGSEDI, your healthcare provider should show you or your caregiver how to use it the right way. If you or your caregiver have any questions, ask your healthcare provider.

Read these instructions for use before you start using your TEGSEDI prefilled syringe and each time you get a repeat prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Each TEGSEDI prefilled syringe has a Safety Syringe Device (SSD), contains one dose and is for one-time use only. Do not use this medication if it shows haziness, particulate matter or discolouration or if the prefilled syringe is leaking. If the solution looks hazy, has particulate matter, discolouration or if the prefilled syringe is leaking, throw the prefilled syringe away in a puncture resistant (Sharps) container, and use a new prefilled syringe.

Parts of the Safety Syringe Device (SSD)



WARNINGS

Do not remove needle cap until you have reached **Step 6** of these instructions and are ready to inject TEGSEDI;
Do not share your syringe with another person or re-use your syringe;
Do not use if dropped onto a hard surface, if damaged, or if the needle is bent;
Do not shake or freeze the prefilled syringe;
Do not use if the expiry date on the side of the syringe body has passed.
If any of the above happens, **throw away** the prefilled syringe in a puncture-resistant (Sharps) container and use a new prefilled syringe.

PREPARATION

1. Gather supplies

- 1 TEGSEDI prefilled syringe from the refrigerator
- 1 Alcohol wipe (not supplied)
- 1 Gauze pad or cotton ball (not supplied)
- 1 Puncture-resistant (Sharps) container (not supplied)

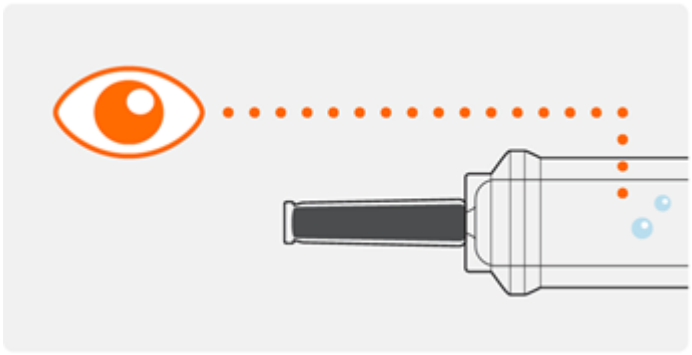
Do not perform the injection without all the supplies listed.

2. Prepare to use your TEGSEDI prefilled syringe

- Remove the plastic tray from the carton and check the expiry date.
- Let TEGSEDI warm up at room temperature (20 °C to 25 °C) for at least 30 minutes before giving the injection.
- Remove the syringe from the tray by holding onto the syringe body.

Do not use if the expiry date has passed.
Do not warm the syringe in any other way. For example, **do not** warm in a microwave or hot water, or near other heat sources.
Do not move the plunger;
Do not remove the syringe from the tray by holding onto the needle cap or plunger.

3. Check medicine in the syringe

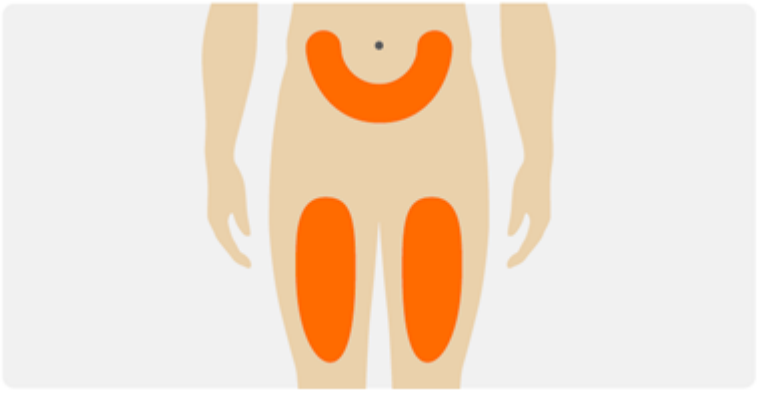


Look in the inspection area to check that the solution is clear and colourless or pale yellow in colour. It is normal to see air bubbles in the solution. You do not need to do anything about it.

Do not use the product if the solution shows haziness, particulate matter, discolouration or leakage.

If the solution looks hazy, has particulate matter, discolouration or leakage, throw the prefilled syringe away in a puncture resistant (Sharps) container, and use a new prefilled syringe.

4. Choose the injection site



Choose an injection site on your abdomen or the front of your thigh.

Do not inject into the 3cm area around the belly-button (navel).

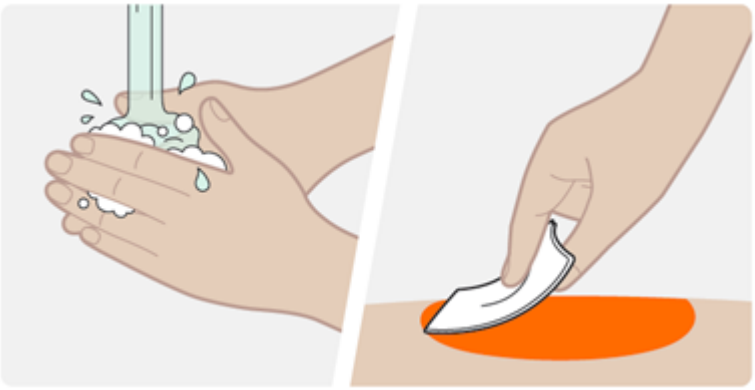
Do not inject into the same site each time.

Do not inject where skin is bruised, tender, red or hard.

Do not inject into scars or damaged skin.

Do not inject through clothing.

5. Clean the injection site



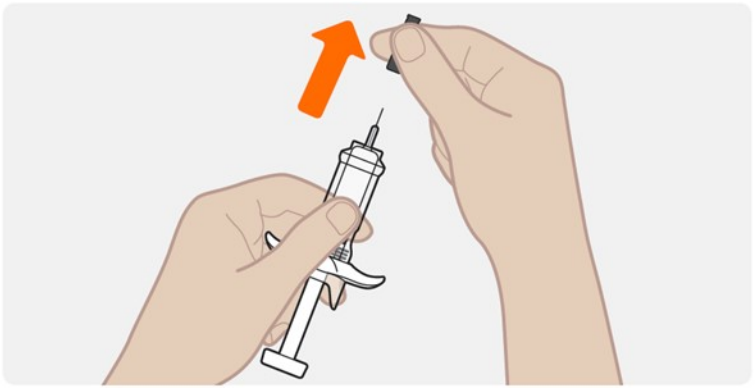
Wash your hands with soap and water.

Clean the injection site with an alcohol wipe in a circular motion. Let the skin air dry.

Do not touch the area again before injecting.

INJECTION

6. Remove the needle cap



Hold the syringe by the body, with the needle facing away from you.

Remove needle cap by pulling it straight off. Do not twist it off.

You may see a drop of liquid at the end of the needle. This is normal.

Keep your hands away from the plunger to avoid pushing the plunger before you are ready to inject.

Do not remove the needle cap until right before you inject.

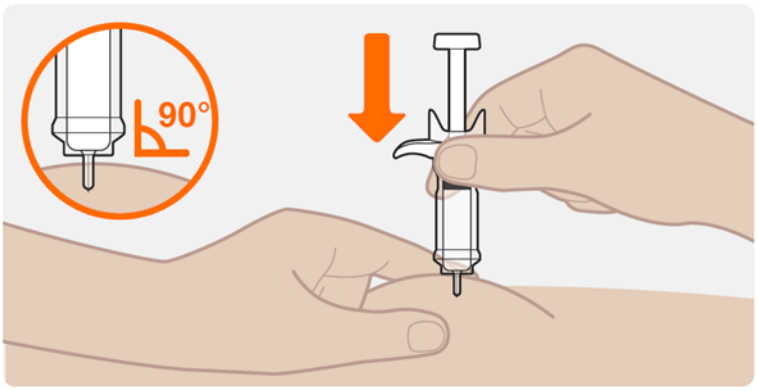
Do not pull the cap off while holding the syringe by the plunger. Always hold by the body of the syringe.

Do not let the needle touch any surface.

Do not remove any air bubbles from the syringe.

Do not put the needle cap back onto the syringe.

7. Insert the needle



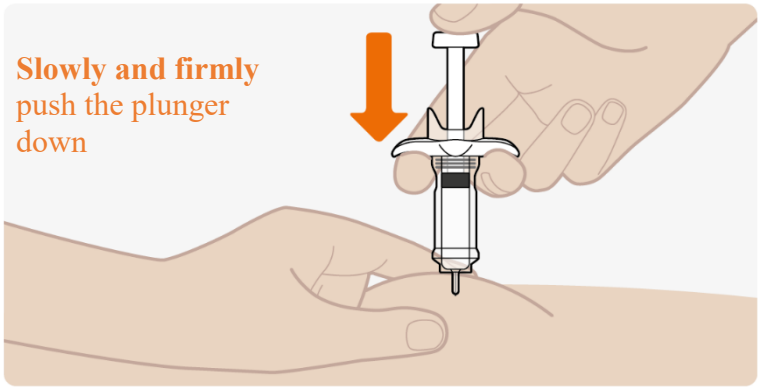
Hold the syringe in 1 hand.

Hold the skin around at the injection site as your healthcare provider has instructed you. You should either gently pinch the skin at the injection site or give the injection without pinching the skin.

Slowly insert the entire needle into the chosen injection site at a 90° angle until fully inserted.

Do not hold the syringe by the plunger or push against the plunger to insert the needle.

8. Start the injection



Slowly and firmly push the plunger all the way down until the medicine is injected. Make sure the needle stays fully inserted in the injection site while you are injecting the medicine.

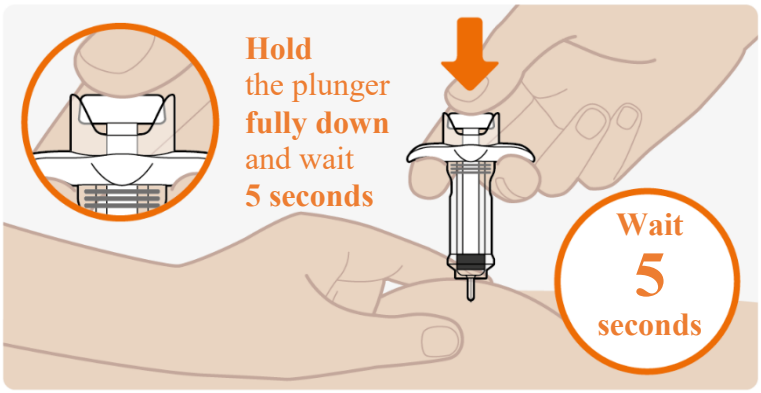
It is important to fully push the plunger all the way down.

Your syringe may make a click sound as you push the plunger down. This is normal. This **does not** mean that the injection is finished.

The plunger can feel stiffer towards the end of the injection. You may need to press a little harder on the plunger to make sure you have pushed it as far as it will go.

Do not let go of the plunger.

9. Push the plunger down

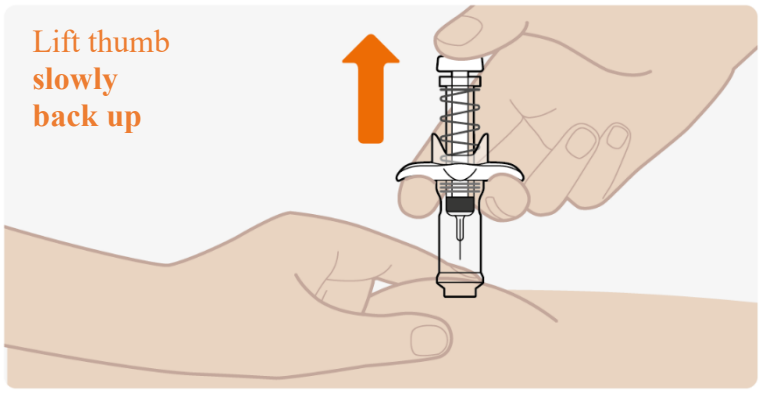


Push firmly on the plunger at the end of the injection. Hold the plunger fully down and wait for 5 seconds. If you let go of the plunger too quickly, you may lose some of the medicine.

The plunger will start to lift automatically which means that the plunger has been pushed fully down.

Press down again if the plunger does not start to lift automatically.

10. Complete the injection



Slowly lift up on the plunger and let the safety spring push the plunger up automatically.

The needle should now be retracted safely inside the syringe, and the safety mechanism spring visible on the outside of the plunger.

When the plunger comes to a stop, your injection is complete.

If the plunger does not rise up automatically when you release the pressure, it means the safety spring did not activate and you should push the plunger again but harder.

Throw away the cap and syringe into the puncture-resistant (Sharps) container right away (See section - "Dispose of the used syringe").

Do not pull the plunger up by hand. Lift the whole syringe straight up.

Do not try to replace the cap on the retracted needle.

Do not rub the injection site.

DISPOSAL AND CARE

Dispose of the used syringe

Put the used TEGSEDI prefilled syringe in a sharps disposal container right away after use. Do not throw away the prefilled syringe in your household waste.

Usual dose:

- 284 mg / 1.5 mL inotersen injected just below your skin once a week.
- Your doctor may change how often you inject your dose depending on the results of your platelet count.
- Each prefilled syringe contains one dose and is for one-time use only.
- Use the entire contents of the syringe.
- Choose the same day of the week to have your dose.
- Your doctor will recommend taking Vitamin A while on TEGSEDI.

Overdose:

If you think you have taken too much TEGSEDI, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you missed a dose of this medication, take it as soon as you remember. But if it is 2 days or less until your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular dosing schedule. Do not take two doses at the same time or dose on consecutive days.

What are possible side effects from using TEGSEDI?

These are not all the possible side effects you may feel when taking TEGSEDI. If you experience any side effects not listed here, contact your healthcare professional.

Very common side effects include the following:

- Thrombocytopenia (low levels of platelets which are blood cells that help your body form clots to stop bleeding)
- Anaemia (Reduction in red blood cells which can make the skin pale and cause weakness or breathlessness)
- Vomiting, or nausea
- Diarrhoea
- Constipation
- Injection site erythema (redness around the injection site), injection site pruritis (injection site itching) or injection site pain
- Fatigue
- Oedema peripheral (swelling of the ankles, feet or fingers)
- Pyrexia (increase in body temperature)
- Chills (Feeling Cold)
- Myalgia (Muscle aches/ pain) or arthralgia (Joint pain)
- Headache

Common side effects include the following:

- Eosinophilia (An increase in the number of white blood cells called eosinophils in your blood which help fight infection)
- Chest pain or heart disorders, such as atrial fibrillation (an irregular heart beat that may increase your risk of stroke, or heart-related complications) or congestive cardiac failure (a condition in which the heart does not pump blood as effectively as it should, often associated with shortness of breath, weakness and swelling of the legs and ankles)
- Balance disorder, or vertigo (feelings of spinning or being off balance or unsteady)
- Hypothyroidism (low level of thyroid hormone which can cause fatigue, feeling cold, weight gain and poor memory and concentration
- Eye disorders, such as cataracts (clouding of the eye lens which can lead to decreased vision), ocular hyperaemia (white part of the eye is bloodshot) or vitreous floaters (visual spots that resemble grey or black specks and can drift across the eyes)
- Dry mouth
- Abdominal distension (swelling or bloating of the belly)
- Gastroesophageal reflux disease (This occurs when acid in the stomach flows back into the food pipe causing heartburn)
- Flu like symptoms such as high temperature, aches and chills

- Peripheral swelling (Swelling of the lower legs or hands)
- Injection site reaction (inflammation or damage to the tissue around the injection site), injection site bruising, swelling, discolouration, rash, haemorrhage (excessive bleeding from the injection site) haematoma (a solid swelling of clotted blood at the injection site) or induration (hardening of the area around the injection site)
- Upper respiratory tract infection (infection in the mouth, nose, throat or voice box)
- Asymptomatic bacteriuria (the presence of bacteria in the urine that does not cause symptoms)
- Skin infection, abrasion or lesion (scrape, graze, abnormal lump, or sore on the skin)
- Localised infection (an infection that affects a specific part of the body or organ)
- Gastroenteritis viral (infection in the stomach and intestines caused by a virus. Symptoms may include diarrhea, cramps and vomiting)
- Contusion (bruise)
- Limb Injury
- Platelet count decreased (decrease in platelets which are blood cells that help your body form clots to stop bleeding)
- Changes to your blood and urine tests (this may indicate injection or liver or kidney damage)
- Decreased appetite
- Dehydration
- Vitamin D deficiency (A lack of vitamin D)
- Back pain, muscle spasms, musculoskeletal pain or stiffness (pain or stiffness that may affect ligaments, tendons, muscles or bones)
- Paraesthesia (pins and needles feeling)
- Syncope (temporary loss of consciousness, or passing out) or loss of consciousness
- Prescyncope (feeling lightheaded or feeling faint)
- Migraine
- Somnolence (sleepiness or drowsiness)
- Depression
- Acute kidney injury, chronic kidney disease or renal impairment/failure
- Dyspnea (shortness of breath)
- Oropharyngeal pain (throat pain)
- Pleural effusion (excess fluid in the lungs that may impair breathing)
- Productive cough (cough that produces phlegm)
- Erythema (redness of skin)
- Hyperhidrosis (excessive sweating)
- Pruritus (itchiness), rash, urticaria (hives) or skin ulcer (open sore on the skin)
- Night sweats
- Skin lesion (abnormal lump, or sore on the skin)
- Changes in blood pressure, including hypertension (high blood pressure) hypotension, (low blood pressure) or orthostatic hypotension (feeling faint or dizzy, or fainting after standing up due to a fall in blood pressure)
- Haematoma (solid collection of blood within the tissues that may look similar to bruising)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON Low number of platelets in your blood. (symptoms such as more frequent or easy bruising, small red spots on the skin, bleeding from the gums, bleeding that will not stop, nosebleeds)		√	
COMMON Kidney inflammation (symptoms such as foaming urine, pink or brown coloured urine, or blood in the urine)		√	
UNKNOWN FREQUENCY **Allergic reaction** (symptoms such as swelling of the face, lip or throat, rash, itchiness, hives, difficulty breathing or wheezing)			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store refrigerated at 2 °C to 8 °C in the original container and protect from light. Remove from refrigerator at least 30 minutes before use. TEGSEDI may be stored unrefrigerated (2 °C to 30 °C) in the original container for up to 6 weeks; if not used within the 6 weeks, throw TEGSEDI away.

Keep out of reach and sight of children.

If you want more information about TEGSEDI:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); the manufacturer's website http://www.akceatx.ca/, or by calling 1-833-327-0723.

This leaflet was prepared by Akcea Therapeutics, Inc.

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