swissmedic

Date: 8 October 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

TEGSEDI®

International non-proprietary name: inotersen

Pharmaceutical form: solution for injection in pre-filled syringe

Dosage strength(s): 284 mg inotersen (as inotersen sodium) in 1.5 mL of solution

Route(s) of administration: subcutaneous administration

Marketing authorisation holder: SFL Pharma GmbH (now Swedish Orphan Biovitrum AG, Basel)

Marketing authorisation no.: 67451

Decision and decision date: approved on 31.05.2021

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
hATTR	Hereditary transthyretin amuloidosis
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
TTR	Transthyretin

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for inotersen in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a[decies] no. 2 of the TPA. Orphan drug status was granted on 25.04.2019.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Tegsedi is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR).

2.2.2 Approved indication

Tegsedi is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR).

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose is 284 mg inotersen by subcutaneous injection. Doses should be administered once every week. For consistency of dosing, patients should be instructed to receive the injection on the same day every week.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	27 June 2019
Formal control completed	23 July 2019
List of Questions (LoQ)	20 November 2019
Response to LoQ	13 February 2020
Preliminary decision	13 May 2020
Response to preliminary decision	13 September 2020
Final decision	31 May 2021
Decision	approval

Swissmedic has not assessed the primary data of this application and relies for its decision on the assessment of the foreign reference authority, the EMA. The current SwissPAR relates to the publicly available assessment report Tegsedi (inotersen) (EMA/381704/2018, published 06.08.2018), issued by the EMA.

3 Medical context

Hereditary transthyretin amyloidosis (hATTR) is a progressive disease caused by mutations in the gene that codes for transthyretin (TTR). Single-point gene mutations destabilise the normal tetrameric structure of the TTR protein, causing its dissociation into free monomers and subsequent aggregation into insoluble, extracellular amyloid fibril deposits. These deposits accumulate in multiple organs, resulting in severe damage to cells, especially in the peripheral nerves and the heart.

Approved treatments for hATTR in Switzerland:

- Vyndaqel (tafamidis) was approved in March 2020 and is indicated for the treatment of transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related hospitalisation. Tafamidis binds to the 2 thyroxine binding sites on the native tetrameric form of TTR, preventing dissociation into monomers (for details see www.swissmedicinfo.ch).

- Onpattro (patisiran) was approved in September 2019 for the treatment of hereditary transthyretin amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy. Patisiran is a double-stranded small interfering ribonucleic acid (siRNA). Through a natural process called RNA interference (RNAi), patisiran causes the catalytic degradation of TTR mRNA in the liver, resulting in a reduction of serum TTR protein.

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and relies on the assessment of the foreign reference authority, the EMA. The current SwissPAR relating to quality aspects refers to the publicly available Assessment Report Tegsedi (inotersen) (EMA/381704/2018, published 06.08.2018), issued by the EMA.

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The preclinical aspects in this SwissPAR refer to the publicly available assessment report Tegsedi (inotersen) (EMA/381704/2018, published 06.08.2018), issued by the EMA.

6 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority the EMA. The clinical aspects in this SwissPAR refer to the publicly available assessment report Tegsedi (inotersen) (EMA/381704/2018, published 06.08.2018), issued by the EMA.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Tegsedi was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the *"Undesirable effects"* section for advice on the reporting of adverse reactions.

TEGSEDI®

Composition

Active substances

284 mg inotersen (as sodium) solution for injection in pre-filled syringe

Excipients

Water for injections
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

Pharmaceutical form and active substance quantity per unit

Solution for injection in pre-filled syringe
Clear, colourless to pale yellow solution (pH 7.5 – 8.8)
Each pre-filled syringe contains 284 mg inotersen in a volume of 1.5 ml
Subcutaneous administration

Indications/Uses

Tegsedi is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR).

Dosage/Administration

The therapy should be initiated in a center for neuromuscular diseases, under the supervision of a physician experienced in the treatment of patients with hereditary transthyretin amyloidosis. Continued treatment should also be followed by a physician experienced in the treatment of transthyretin amyloidosis.

Usual dosage

The recommended dose is 284 mg inotersen by subcutaneous injection. Doses should be administered once every week. For consistency of dosing, patients should be instructed to receive the injection on the same day every week.

Dose adjustment following undesirable effects/ interactions

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 (x10^9/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.
< 75*	Twice weekly until 3 successive values above 75 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 antiplatelet 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 stop and reverse the platelet decline. Patients who discontinue therapy with Tegsedi due to platelet counts below 25 x 10^9/L should not reinitiate therapy.

Patients with impaired hepatic function

No dose adjustment is required for patients with mild or moderate hepatic impairment (see section *"Pharmacokinetics"*). Tegsedi must not be used in patients with severe hepatic impairment (see section "*Contraindications*").

Patients undergoing liver transplant

Tegsedi has not been evaluated in patients undergoing liver transplant. It is, therefore, recommended that dosing of Tegsedi should be discontinued in subjects undergoing liver transplantation (see section "*Warnings and precautions*").

Patients with impaired renal function

No dose adjustment is required for patients with mild or moderate renal impairment (see section "*Pharmacokinetics*"). Tegsedi should not be used in patients with a urine protein to creatinine ratio (UPCR) ≥ 113 mg/mmol (1 g/g) or estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73m^2(see section "*Contraindications*").

Because of the risk of glomerulonephritis and possible renal function decline, UPCR and eGFR should be monitored during treatment with Tegsedi (see section "*Warnings and precautions*"). If acute glomerulonephritis is confirmed, the treatment should be permanently discontinued.

Elderly patients

No dose adjustment is required in patients aged 65 and over (see section "*Pharmacokinetics*").

Children and adolescents

The safety and efficacy of Tegsedi in children and adolescents below 18 years of age have not been established. No data are available.

Delayed administration

If a dose of Tegsedi is missed, then the next dose should be administered as soon as possible, unless the next scheduled dose is within two days, in which case the missed dose should be skipped and the next dose administered as scheduled.

Administration schedule

Doses should be administered once every week. For consistency of dosing, patients should be instructed to receive the injection on the same day every week.

Mode of administration

Subcutaneous use 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.
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.
The pre-filled syringe should be allowed to reach room temperature prior to injection. It should be removed from refrigerated storage at least 30 minutes before use. Other warming methods should not be used.

Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section *"Composition"*).
Platelet count < 100 x 10^9/L prior to treatment.
Urine protein to creatinine ratio (UPCR) ≥ 113 mg/mmol (1 g/g) prior to treatment.
Estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73m^2.
Severe hepatic impairment.

Warnings and precautions

Precautions prior to initiation of Tegsedi

Platelet count, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR) and hepatic enzymes should be measured prior to treatment with Tegsedi.
Transient increases of CRP and platelet levels may occur in some patients after initiation of Tegsedi. This reaction typically resolves spontaneously after a few days of treatment.

Thrombocytopenia

Tegsedi is associated with reductions in platelet count, which may result in thrombocytopenia (see section *"Undesirable effects"*). 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 section "*Dosage/Administration*").

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, in patients taking anithrombotic medicinal products, antiplatelet medicinal products, or medicinal products that may lower platelet count (see section *"Interactions"*), and in patients with prior history of major bleeding events.

Glomerulonephritis/ renal function decline

Glomerulonephritis has occurred in patients treated with Tegsedi (see section *"Undesirable effects"*). Cases of glomerulonephritis were accompanied by nephrotic syndrome. Possible complications of nephrotic syndrome can include oedema, hypercoagulability with venous or arterial thrombosis, and increased susceptibility to infection. Tegsedi-treated patients who develop glomerulonephritis will require monitoring and treatment for nephrotic syndrome and its manifestations. Renal function decline has also been observed in a number of subjects without signs of glomerulonephritis (see section *"Undesirable effects"*).

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 greater than 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 (see section "*Contraindication*").

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 (see section "*Interactions*").

Vitamin A deficiency

Based on the mechanism of action, Tegsedi is expected to reduce plasma vitamin A (retinol) below normal levels (see section *"Mechanism of action"*).

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

Patients receiving Tegsedi should take oral supplementation of approximately 3,000 IU vitamin A per day in order to reduce the potential risk of ocular toxicity due to vitamin A deficiency. Referral for ophthalmological assessment is recommended if patients develop ocular symptoms consistent with vitamin A deficiency, incuding: reduced night vision or night blindness, persistent dry eyes, eye inflammation, corneal inflammation or ulceration, corneal thickening, corneal perforation.

During the first 60 days of pregnancy, both too high and too low vitamin A levels may be associated with an increased risk of foetal malformation. Therefore, pregnancy should be excluded before treatment initiation and women of childbearing potential should practise effective contraception (see section *"Pregnancy, Lactation"*). If a woman intends to become pregnant, Tegsedi and vitamin A supplementation should be discontinued and plasma vitamin A levels should be monitored and have returned to normal before conception is attempted.

In the event of an unplanned pregnancy, Tegsedi should be discontinued. Due to the long half-life of Tegsedi (see section *"Pharmacokinetics"*), a vitamin A deficit may even develop after cessation of treatment. No recommendation can be given whether to continue or discontinue vitamin A supplementation during the first trimester of an unplanned pregnancy. If vitamin A supplementation is continued, the daily dose should not exceed 3000 IU per day, due to the lack of data supporting higher doses. Thereafter, vitamin A supplementation of 3000 IU per day should be resumed in the second and third trimester if plasma retinol levels have not yet returned to normal, because of the increased risk of vitamin A deficiency in the third trimester.

It is not known whether vitamin A supplementation in pregnancy will be sufficient to prevent vitamin A deficiency if the pregnant female continues to receive Tegsedi. However, increasing vitamin A supplementation to above 3000 IU per day during pregnancy is unlikely to correct plasma retinol levels due to the mechanism of action of Tegsedi and may be harmful to the mother and foetus.

Liver monitoring

Hepatic enzymes should be measured 4 months after initiation of treatment with Tegsedi and annually thereafter or more frequently as clinically indicated, in order to detect cases of hepatic impairment (see section "*Undesirable effects*").

Liver transplant rejection

Tegsedi was not evaluated in patients undergoing liver transplantation in clinical trials (see section "*Dosage/Administration*").

In a completed expanded access program, reversible rejection has been identified in patients who have had prior liver transplantation and were being treated with Tegsedi for progressive hATTR disease. Three patients suffered from acute liver transplant rejection, one 17 years after liver transplant but less than two months after starting inotersen, another 11 years after liver transplant and 5 months after starting inotersen, and the third 8 years after liver transplant but 8 weeks after starting inotersen (the latter in the context of an immunosuppressive weaning off study). In these cases, the patients clinically improved and transaminase levels normalized after glucocorticoid administration and cessation of Tegsedi.

Patients with prior liver transplant should be monitored monthly for signs and symptoms of transplant rejection, including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin, during treatment with Tegsedi. Discontinuation of Tegsedi should be considered in patients who develop liver transplant rejection during treatment.

Stroke and Cervicocephalic Arterial Dissection

In clinical studies, 1 of 161 (0.6%) Tegsedi-treated patients experienced carotid artery dissection and stroke. These events occurred within 2 days of the first Tegsedi dose, a time when the patient also had symptoms of cytokine release (e.g., nausea, vomiting, muscular pain and weakness) and a high sensitivity C-reactive protein level greater than 100 mg/L.

Inflammatory and Immune Effects

Inflammatory and immune changes are an effect of some antisense oligonucleotide drugs, including Tegsedi. In clinical studies, serious inflammatory and immune adverse reactions occurred in Tegsedi-treated patients, including immune thrombocytopenia and glomerulonephritis, as well as a single case of antineutrophil cytoplasmic autoantibody (ANCA)-positive systemic vasculitis (see *"Glomerulonephritis / renal function decline"*).

Neurologic Serious Adverse Reactions

In clinical studies, neurologic serious adverse reactions consistent with inflammatory and immune effects occurred in Tegsedi-treated patients, in addition to stroke and carotid artery dissection (see "*Inflammatory and Immune Effects*"). Two months after the first Tegsedi dose, one patient developed a change in gait that progressed over 6 months to paraparesis, in the absence of radiologic evidence of spinal cord compression. Another patient developed progressive lumbar pain, weight loss, headache, vomiting, and impaired speech 7 months after starting Tegsedi. Cerebrospinal fluid analysis findings

included elevated protein, a lymphocyte-predominant pleocytosis, and testing that was negative for infection. The patient recovered after empiric therapy (high-dose steroids, antibiotics) and resumed Tegsedi without recurrence of symptoms.

Interactions

Caution should be used with antithrombotic medicinal products, antiplatelet medicinal products, and medicinal products that may lower platelet count, for example acetylsalicyclic acid, clopidogrel, warfarin, heparin, low-molecular weight heparins, Factor Xa inhibitors such as rivaroxaban and apixaban, and thrombin inhibitors such as dabigatran (see section "*Warnings and precautions*").
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 opiods (see section "*Warnings and precautions*"). Although the population PK analysis did not identify clinically relevant effects of some nephrotoxic medicines on the clearance of Tegsedi or on the potential for an effect on renal function, a systematic assessment of co-administration of Tegsedi and potentially nephrotoxic medicinal products has not been conducted.

Pregnancy, lactation

Women of child-bearing potential

Tegsedi will reduce the plasma levels of vitamin A, which is crucial for normal foetal development. It is not known whether vitamin A supplementation will be sufficient to reduce the risk to the foetus (see section "*Warnings and precautions*"). For this reason, pregnancy should be excluded before initiation of Tegsedi therapy and women of child-bearing potential should practise effective contraception.

Pregnancy

There are no or limited amount of data from the use of Tegsedi in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section"*Preclinical data*"). Due to the potential teratogenic risk arising from unbalanced vitamin A levels, Tegsedi should not be used during pregnancy, unless the clinical condition of the woman requires treatment with Tegsedi. Women of child-bearing potential have to use effective contraception during treatment with Tegsedi.

Lactation

It is unknown whether Tegsedi/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of Tegsedi metabolites in milk (see section "*Preclinical data*"). A risk to the breastfed newborn/infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Tegsedi therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There is no information available on the effects of Tegsedi on human fertility. Animal studies did not indicate any impact of Tegsedi on male or female fertility.

Effects on ability to drive and use machines

Tegsedi has no or negligible influence on the ability to drive and use machines.

Undesirable effects

The most frequently observed adverse reactions during treatment with Tegsedi were events associated with injection site reactions (50.9%). Other most commonly reported adverse reactions with Tegsedi were nausea (31.3%), headache (23.2%), pyrexia (19.6%), peripheral oedema (18.8%), chills (17.9%), vomiting (15.2%), thrombocytopenia (13.4%) anaemia (13.4%), and platelet count decreased (10.7%). Table 2 presents the adverse reactions (ADRs) listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each ADR is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 2. List of adverse reactions in clinical studies

System Organ Class	Very Common	Common	Uncommon
Blood and lymphatic system disorders	Thrombocytopenia (13.4%) Anaemia (13.4%) Platelet count decreased (10.7%)	Eosinophilia	
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders		Decreased appetite	
Nervous system disorders	Headache (23.2%)		
Vascular disorders		Orthostatic hypotension Hypotension Haematoma	
Gastrointestinal disorders	Nausea (31.3%)		

System Organ Class	Very Common	Common	Uncommon
	Vomiting (15.2%)		
Hepatobiliary disorders		Transaminases increased	
Skin and subcutaneous disorders		Pruritus Rash	
Renal and urinary disorders		Glomerulonephritis Proteinuria Renal failure Acute kidney injury Renal impairment	
General disorders and administration site conditions	Injection site reactions (50.9%) Pyrexia (19.6%) Peripheral oedema (18.8%) Chills (17.9%)	Influenza like illness Peripheral swelling Injection site discolouration	
Injury, poisoning and procedural complications		Contusion	

Description of selected undesirable effects

Injection site reactions

The most frequently observed events included events associated with injection site reactions (includes injection site pain, erythema, pruritus, swelling, rash, induration, bruising and haemorrhage). These events are usually either self-limiting or can be managed using symptomatic treatment.

Thrombocytopenia

Tegsedi is associated with reductions in platelet count, which may result in thrombocytopenia. In the Phase 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 ans precautions*”).

Glomerulonephritis / renal function decline

Patients should be monitored for signs of increased proteinuria and reduction in eGFR during treatment with Tegsedi (see *”Warnings ans precautions”*).

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. Development of anti-drug antibodies to Tegsedi was

characterised by late onset (median onset > 200 days) and low titer (median peak titer of 284 in the pivotal study). 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.

Reporting suspected adverse events

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Properties/Effects

ATC code

N07XX15

Mechanism of action

Inotersen is a *2′-O*-2-methoxyethyl (2′-MOE) phosphorothioate antisense oligonucleotide (ASO) inhibitor of human transthyretin (TTR) production. The selective binding of inotersen to the TTR messenger RNA (mRNA) causes the degradation of both mutant and wild type (normal) TTR mRNA. This prevents the synthesis of TTR protein 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 principal carrier of vitamin A (retinol). Therefore, reduction in plasma TTR is expected to result in reduction of plasma retinol levels to below the lower limit of normal.

Pharmacodynamics

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 ranging from 68.41% to 74.03% (median range: 74.64% to 78.98%) from

Week 13 to Week 65 (Figure 1). In the placebo group, mean serum TTR concentration decreased by 8.50% at Week 3 and then remained fairly constant throughout the treatment period.

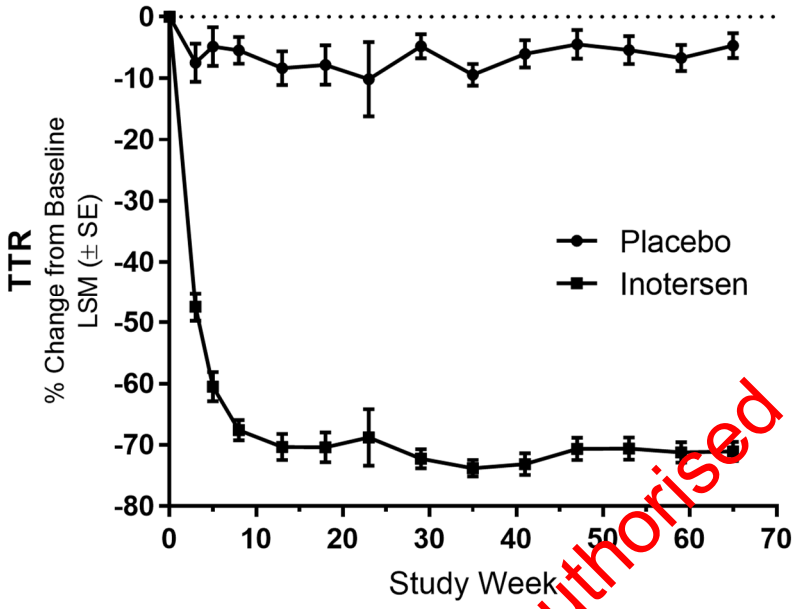

Figure 1 Percent Change from Baseline in Serum TTR Over Time

Clinical efficacy

The NEURO-TTR multicentre, double-blind, placebo-controlled trial was comprised of 172 treated patients with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN). The disease hATTR-PN is classified into 3 stages such that i) Stage 1 patients do not require assistance with ambulation, ii) Stage 2 patients do require assistance with ambulation, and iii) Stage 3 patients are bound to wheelchair. Patients with Stage 1 and Stage 2 hATTR-PN and an NIS ≥10 and ≤130 were recruited in the pivotal NEURO-TTR study. The study evaluated 284 mg Tegsedi administered as one subcutaneous injection once per week, for 65 weeks of treatment. Patients were randomised 2:1 to receive either Tegsedi or placebo. The primary efficacy endpoints were the change from baseline to Week 66 in the modified Neuropathy Impairment Score + 7 tests (mNIS+7) composite score and in the Norfolk Quality of Life – Diabetic Neuropathy (QoL-DN) questionnaire total score. 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). Baseline demographic and disease characteristics are shown in Table 3.

Table 3. Baseline demographics

	Placebo (N=60)	Tegsedi (N=112)
Age (years), mean (SD)	59.5 (14.05)	59.0 (12.53)

	Placebo (N=60)	Tegsedi (N=112)
Age 65 years and older, n (%)	26 (43.3)	48 (42.9)
Male, n (%)	41 (68.3)	77 (68.8)
mNIS+7, mean (SD)	74.75 (39.003)	79.16 (36.958)
Norfolk QoL-DN, mean (SD)	48.68 (26.746)	48.22 (27.503)
Disease stage, n (%) Stage 1 Stage 2	 42 (70.0) 18 (30.0)	 74 (66.1) 38 (33.9)
V30M TTR mutation[1], n (%) Yes No	 33 (55.0) 27 (45.0)	 56 (50.0) 56 (50.0)
Previous treatment with tafamidis or diflunisal[1], n (%) Yes No	 36 (60.0) 24 (40.0)	 63 (56.3) 49 (43.8)
hATTR-CM[2], n (%)	33 (55.0)	75 (66.4)
hATTR-PN Disease Duration[3] (months) mean (SD)	64.0 (52.34)	63.9 (53.16)
hATTR-CM Disease Duration[3] (months) mean (SD)	34.1 (29.33)	44.7 (58.00)

[1] Based on clinical database

[2] Defined as all patients with a diagnosis of hereditary transthyretin amyloidosis with cardiomyopathy (hATTR-CM) at study entry or left ventricular wall thickness >1.3 cm on echocardiogram without a known history of persistent hypertension.

[3] Duration from symptom onset to informed consent date

The changes from baseline in both primary endpoints (mNIS+7 and Norfolk QoL-DN) demonstrated statistically significant benefit in favour of Tegsedi treatment at Week 66 (Table 4). Results across multiple disease characteristics [TTR mutation (V30M, non-V30M)], disease stage (Stage 1, Stage 2), previous treatment with tafamidis or diflunisal (yes, no), presence of hATTR-CM (yes, no) at Week 66 showed statistically significant benefit in all subgroups based on mNIS+7 composite score and all but one of these subgroups (ECM-Echo Set; p=0.067) based on Norfolk QoL-DN total score (Table 5). 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 (Figure 2).

Table 4. 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 Mean (SD)	 60 74.75 (39.003)	 112 79.16 (36.958)	 59 48.68 (26.746)	 111 48.22 (27.503)
Week 66 Change n LSM (SE) 95% CI Difference in LSM (Tegsedi – Placebo) 95% CI P-value	 60 25.43 (3.225) 19.11, 31.75	 112 10.54 (2.397) 5.85, 15.24 -14.89 -22.55, 7.22 <0.001	 59 12.94 (2.840) 7.38, 18.51	 111 4.38 (2.175) 0.11, 8.64 -8.56 -15.42, -1.71 0.015

Table 5. Subgroup Analysis of mNIS+7 and Norfolk QoL-DN

	mNIS+7			Norfolk QoL-DN		
		Change from Baseline Tegsedi – Placebo			Change from Baseline Tegsedi – Placebo	
Subgroup	n (Placebo, Tegsedi)	LSM Difference (SE)	P-value	n (Placebo, Tegsedi)	LSM Difference (SE)	P-value
Week 66						
V30M	32, 58	13.52 (3.795)	p<0.001	32, 58	-8.14 (3.998)	p=0.042
Non-V30	28, 54	19.06 (5.330)	p<0.001	27, 53	-9.87 (4.666)	p=0.034
Stage I Disease	39, 74	-12.13 (3.838)	P=0.002	38, 73	-8.44 (3.706)	p=0.023
Stage II Disease	21, 38	-24.79 (5.601)	p<0.001	21, 38	-11.23 (5.271)	p=0.033
Previous use of stabilisers	33, 61	-18.04 (4.591)	p<0.001	32, 60	-9.26 (4.060)	p=0.022
Treatment naïve	27, 51	-14.87 (4.377)	p<0.001	27, 51	-10.21 (4.659)	p=0.028
CM-Echo Set	33, 75	-14.94 (4.083)	p<0.001	33, 75	-7.47 (4.075)	p=0.067
Non-CM-Echo Set	27, 37	-18.79 (5.197)	p<0.001	26, 36	-11.67 (4.213)	p=0.006

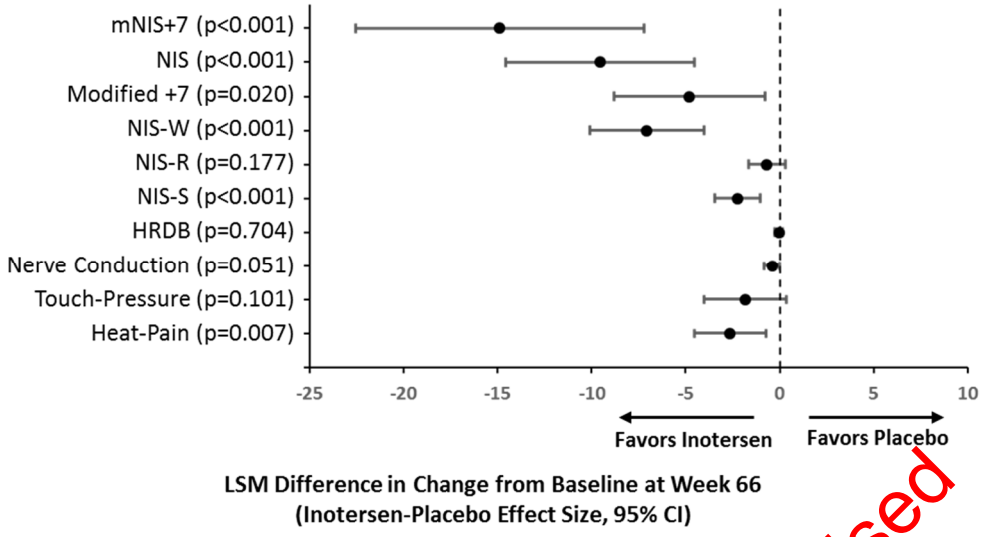

Figure 2 Difference in Least Squares Mean (LSM) Change from Baseline Between Treatment Groups in mNIS+7 and Components

A responder analysis of mNIS+7 using thresholds ranging from a 0- to 30-point increase from baseline (using the safety set), showed the Tegsedi group had approximately a 2-fold higher response rate than the placebo group at each threshold tested, demonstrating consistency of response. A responder was defined as a patient who had a change from baseline that was less than or equal to the threshold value. Patients that had terminated the treatment early irrespective of the reason or had missing week 66 data were considered as non-responders. Statistical significance in favour of Tegsedi was demonstrated at all thresholds beyond a 0-point change.

Safety and efficacy in paediatric patients

The safety and efficacy of Tegsedi in children and adolescents below 18 years of age have not been established. No data are available.

The European Medicines Agency has waived the obligation to submit the results of studies with Tegsedi in all subsets of the paediatric population in transthyretin amyloidosis (see section "*Dosage/Administration*" for information on paediatric use).

Pharmacokinetics

Absorption

Following subcutaneous administration, Tegsedi is absorbed rapidly into systemic circulation in a dose-dependent fashion with the median time to maximum plasma concentrations (C_{max}) of Tegsedi typically reached within 2 to 4 hours.

Distribution

Tegsedi is highly bound to human plasma protein (> 94%) and the fraction bound is independent of drug concentration. The apparent volume of distribution of Tegsedi at steady-state is 293 L in patients with hATTR. The high volume of distribution suggests Tegsedi extensively distributes into tissues following SC administration.

Metabolism

Inotersen is not a substrate for CYP450 metabolism, and is metabolised in tissues by endonucleases to form shorter inactive oligonucleotides that are the substrates for additional metabolism by exonucleases. Unchanged inotersen is the predominant circulating component.

Elimination

The elimination of inotersen involves both metabolism in tissues and excretion in urine. Both inotersen and its shorter oligonucleotide metabolites are excreted in human urine. Urinary recovery of the parent medicinal product is limited to less than 1% within the 24 hours post dose. Following subcutaneous administration, elimination half-life for inotersen is approximately 1 month.

Kinetics in specific patient groups

Based on the population pharmacokinetic analysis, age, body weight, sex or race has no clinically relevant effect on inotersen exposures. Definitive assessments were limited in some cases as covariates were limited by the overall low numbers.

Hepatic impairment

The pharmacokinetics of inotersen in patients with hepatic impairment has not been studied. Inotersen is not primarily cleared by metabolism in the liver, not a substrate for CYP450 oxidation, and metabolized broadly by nucleases in all tissues of distribution. Thus, pharmacokinetics should not be altered in mild to moderate hepatic impairment.

Renal impairment

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

Elderly patients

No overall differences in pharmacokinetics were observed between other adult and elderly patients.

Preclinical data

Long-term toxicity (or repeat dose toxicity)

Decreased platelet counts were observed in chronic toxicity studies in mice, rats and monkeys at 1.4 to 2.2-fold the human AUC at the recommended therapeutic inotersen dose. Severe platelet declines in association with increased bleeding or bruising were observed in individual monkeys. Platelet counts returned to normal when treatment was stopped but dropped to even lower levels when inotersen administration was resumed. This suggests an immunologically related mechanism.
Extensive and persistent uptake of inotersen was observed by various cell types in multiple organs of all tested animal species including monocytes/macrophages, kidney proximal tubular epithelia, Kupffer cells of the liver, and histiocytic cell infiltrates in lymph nodes and injection sites. The kidney accumulation of inotersen was associated with proteinuria in rats at 13.4-fold the human AUC at the recommended therapeutic inotersen dose. In addition, reduced thymus weight due to lymphocyte depletion was observed in mice and rats. In monkeys, perivascular cell infiltration by lymphohistiocytic cells in multiple organs was noted. These pro-inflammatory organ changes were observed at 1.4 to 6.6-fold the human AUC at the recommeded therapeutic dose in all animal species tested and were accompanied by increases of various plasma cytokines/chemokines.

Carcinogenicity

Tegsedi did not exhibit genotoxic potential *in vitro* and *in vivo* and was not carcinogenic in transgenic rasH2 mice.
Subcutaneous administration of inotersen to Sprague-Dawley rats for up to 94 weeks at doses of 0.5, 2, and 6 mg/kg/week resulted in a dose-related incidence of subcutaneous pleomorphic fibrosarcoma and subcutaneous fibrosarcoma (monomorphic type) at 2 and 6 mg/kg/week in the injection site or injection site regions. The human relevance of these findings is considered to be low.

Reproductive toxicity

Inotersen showed no effects on fertility, embryo-foetal, or postnatal development in mice and rabbits at approximately 3-fold the maximum recommended human equivalent dose. Milk transfer of inotersen was low in mice. However, inotersen is not pharmacologically active in mice and rabbits. Consequently, only effects related to the chemistry of inotersen could be captured in these investigations. Still, no effect on embryo-foetal development was noted with a mouse-specific analogue of inotersen in mice, which was associated with ~60% inhibition (individual range up to 90% reduction) of TTR mRNA expression.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Tegsedi may be stored unrefrigerated for up to 6 weeks below 30 °C. If not used within 6 weeks, it should be discarded.

Special precautions for storage

Store in the refrigerator (2-8°C).
Do not freeze

Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Instructions for handling

Tegsedi should be inspected visually prior to administration. The solution should be clear and colourless to pale yellow. If the solution is cloudy or contains visible particulate matter, the contents must not be injected.
Each pre-filled syringe should be used only once and then placed in a sharps disposal container for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

67451 (Swissmedic)

Packs

1.5 mL solution in a clear Type 1 glass pre-filled syringe.
Tray with tear-off lid.

Pack sizes of:

1 pre-filled syringe [B] (Currently not available on the market.).

4 pre-filled syringes [B].

Marketing authorisation holder

SFL Pharma GmbH

CH-4053 Basel

Switzerland

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