SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tegsedi 284 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 189 mg inotersen (as inotersen sodium).
Each pre-filled syringe contains 284 mg inotersen (as inotersen sodium) in 1.5 mL of solution.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection)

Clear, colourless to pale yellow solution (pH 7.5 – 8.8)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

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

Table 1. Inotersen monitoring and dosing recommendations according to 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. More frequent monitoring should be considered 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. Corticosteroids should be considered if additional risk factors for bleeding are present.
< 25†	Daily until 2 successive values above 25. Then twice weekly monitoring 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 reverse the platelet decline. Patients who discontinue therapy with inotersen due to platelet counts below 25 x 10^9/L should not reinitiate therapy.

Missed doses
If a dose of inotersen 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.

Special populations

Elderly
No dose adjustment is required in patients aged 65 years and over (see section 5.2).

Renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment (see section 5.2). Inotersen 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/1.73 m^2 (see section 4.3).

Because of the risk of glomerulonephritis and possible renal function decline, UPCR and eGFR should be monitored during treatment with inotersen (see section 4.4). If acute glomerulonephritis is confirmed, permanent discontinuation of the treatment should be considered.

Hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment (see section 5.2). Inotersen must not be used in patients with severe hepatic impairment (see section 4.3).

Patients undergoing liver transplant

Inotersen has not been evaluated in patients undergoing liver transplant. It is, therefore, recommended that inotersen should be discontinued in subjects undergoing liver transplantation.

Paediatric population

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

Method of administration

Subcutaneous use only. Each pre-filled syringe is for one-time 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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/1.73 m^2 .

Severe hepatic impairment.

4.4 Special warnings and precautions for use

Thrombocytopenia

Inotersen is associated with reductions in platelet count, which may result in thrombocytopenia at any time during treatment (see section 4.8). Platelet count should be monitored every 2 weeks during the entire course of treatment with inotersen and for 8 weeks following discontinuation of treatment. Recommendations for adjustments to monitoring frequency and inotersen dosing are specified in Table 1 (see section 4.2).

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, bleeding from the gums, blood in urine or stools, bleeding in the whites of eyes), neck stiffness or atypical severe headache because these symptoms may be caused by bleeding in the brain.

Special caution should be used in elderly patients, in patients taking antithrombotic medicinal products, antiplatelet medicinal products, or medicinal products that may lower platelet count (see section 4.5), and in patients with prior history of major bleeding events.

Glomerulonephritis/ renal function decline

Glomerulonephritis has occurred in patients treated with inotersen (see section 4.8). Renal function decline has also been observed in a number of subjects without signs of glomerulonephritis (see section 4.8).

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 inotersen 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 inotersen should be paused while further evaluation for acute glomerulonephritis is performed. Inotersen 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 4.3).

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 4.5).

Vitamin A deficiency

Based on the mechanism of action, inotersen is expected to reduce plasma vitamin A (retinol) below normal levels (see section 5.1).

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 inotersen.

Patients receiving inotersen 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, including: 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 4.6). If a woman intends to become pregnant, inotersen 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, inotersen should be discontinued. Due to the long half-life of inotersen (see section 5.2), 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 3 000 IU per day, due to the lack of data supporting higher doses. Thereafter, vitamin A supplementation of 3 000 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 inotersen. However, increasing vitamin A supplementation to above 3 000 IU per day during pregnancy is unlikely to correct plasma retinol levels due to the mechanism of action of inotersen and may be harmful to the mother and foetus.

Liver monitoring and drug-induced liver injury

Elevated transaminases occur commonly in patients treated with inotersen. Serious cases of drug induced liver injury (DILI) have also been reported, including cases with a long time to

onset (up to 1 year). Liver function should be assessed before initiating treatment with inotersen. Hepatic enzymes should be measured 4 months after initiation of treatment with inotersen and annually thereafter or more frequently as clinically indicated. Prompt clinical evaluation and measurement of liver function tests should be performed preferably within 72 hours in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dose interruption should be considered until clinical and liver function evaluation is performed. If a patient is suspected to have developed liver injury induced by inotersen, inotersen should be permanently discontinued.

Inotersen must not be used in patients with severe hepatic impairment (see sections 4.2 and 4.3).

Liver transplant rejection

Inotersen was not evaluated in patients undergoing liver transplantation in clinical trials (section 4.2). Cases of liver transplant rejection have been reported in patients treated with inotersen. Patients with a prior liver transplant should be monitored for signs and symptoms of transplant rejection during treatment with inotersen. In these patients liver function tests should be performed monthly. Discontinuation of inotersen should be considered in patients who develop liver transplant rejection during treatment.

Precautions prior to initiation of inotersen

Platelet count, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), hepatic enzymes, pregnancy and vitamin A levels should be measured prior to treatment with Tegsedi.

Transient increases of C-reactive protein (CRP) and platelet levels may occur in some patients after initiation of inotersen. This reaction typically resolves spontaneously after a few days of treatment.

Sodium Content

This medicinal product contains less than 1 mmol sodium (23 mg) per 1.5 mL, that is to say essentially “sodium free”.

4.5 Interaction with other medicinal products and other forms of interaction

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 sections 4.2 and 4.4).

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 section 4.4). A systematic assessment of co-administration of inotersen and potentially nephrotoxic medicinal products has not been conducted.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Inotersen 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 4.4). For this reason, pregnancy should be excluded before initiation of inotersen therapy and women of child-bearing potential should practise effective contraception.

Pregnancy

There are no or limited amount of data from the use of inotersen in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Due to the potential teratogenic risk arising from unbalanced vitamin A levels, inotersen should not be used during pregnancy, unless the clinical condition of the woman requires treatment with inotersen. Women of child-bearing potential have to use effective contraception during treatment with inotersen.

Breast-feeding

It is unknown whether inotersen/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of inotersen metabolites in milk (see section 5.3). 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 inotersen on human fertility. Animal studies did not indicate any impact of inotersen on male or female fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse reactions during treatment with inotersen were events associated with injection site reactions (50.9%). Other most commonly reported adverse reactions with inotersen were nausea (31.3%), headache (23.2%), pyrexia (19.6%), peripheral oedema (18.8%), chills (17.9%), vomiting (15.2%), anaemia (13.4%), thrombocytopenia (13.4%) and platelet count decreased (10.7%).

Tabulated summary of adverse reactions

Table 2 presents the adverse drug 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); and not known (cannot be estimated from the available data).

Table 2. List of adverse reactions in clinical studies and post-marketing sources

System Organ Class	Very Common	Common	Uncommon	Not known
Blood and lymphatic system disorders	Thrombocytopenia Anaemia Platelet count decreased	Eosinophilia		
Immune system disorders			Hypersensitivity	
Metabolism and nutrition disorders		Decreased appetite		
Nervous system disorders	Headache			
Vascular disorders		Orthostatic hypotension Hypotension Haematoma		
Gastrointestinal disorders	Vomiting Nausea			
Hepatobiliary disorders		Transaminases increased		Drug-induced liver injury
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	Pyrexia Chills Injection site reactions	Influenza like illness Peripheral swelling Injection site		

System Organ Class	Very Common	Common	Uncommon	Not known
	Peripheral oedema	discolouration		
Injury, poisoning and procedural complications		Contusion		

Description of selected adverse reactions

Injection site reactions

The most frequently observed events included those associated with injection site reactions (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

Inotersen 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 inotersen and 13% of placebo patients; reductions to below 100 x 10^9/L were observed in 23% of patients treated with inotersen and 2% of the patients receiving placebo; confirmed platelet counts of < 75 x 10^9/L were observed in 10.7% of inotersen-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 inotersen (see section 4.4).

Immunogenicity
In the pivotal Phase 2/3 study, 30.4% of patients treated with inotersen tested positive for anti-drug antibodies following 15 months of treatment. Development of anti-drug antibodies to inotersen 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 (maximum plasma concentration (C_{max}), area under the curve (AUC) or half-life) and efficacy of inotersen was observed in the presence of anti-drug antibodies, but patients with anti-drug antibodies had more reactions at the injection site.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

United Kingdom
Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Nervous System Drugs, ATC code: N07XX15

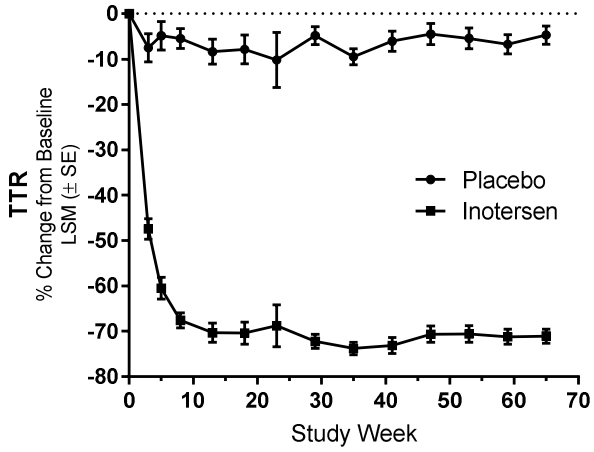
Mechanism of action

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.

Pharmacodynamic effects

In the pivotal study, a phase 2/3 randomized, double-blind, placebo-controlled study to assess the efficacy and safety of ISIS 420915 in patients with Familial Amyloid Polyneuropathy (NEURO-TTR Study), in the inotersen 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.



Transthyretin (TTR)
Least Squares Mean (LSM)
Standard Error (SE)

Figure 1 Percent change from baseline in serum TTR over time

Clinical efficacy and safety

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. Subjects with Stage 1 and Stage 2 hATTR-PN and a Neuropathy Impairment Score (NIS) ≥ 10 and ≤ 130 were recruited in the pivotal NEURO-TTR study. The study evaluated 284 mg inotersen administered as one subcutaneous injection once per week, for 65 weeks of treatment. Patients were randomised 2:1 to receive either inotersen 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)	Inotersen (N=112)
Age (years), mean (SD)	59.5 (14.05)	59.0 (12.53)
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	42 (70.0)	74 (66.1)
Stage 2	18 (30.0)	38 (33.9)
V30M TTR mutation[1], n (%)		
Yes	33 (55.0)	56 (50.0)
No	27 (45.0)	56 (50.0)
Previous treatment with tafamidis or diflunisal[1], n (%)		
Yes	36 (60.0)	63 (56.3)
No	24 (40.0)	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

modified Neuropathy Impairment Score (mNIS)

Quality of Life-Diabetic Neuropathy (QoL-DN)

hereditary transthyretin amyloidosis-polyneuropathy (hATTR-PN)

Standard deviation (SD)

The changes from baseline in both primary endpoints (mNIS+7 and Norfolk QoL-DN) demonstrated statistically significant benefit in favour of inotersen 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 (CM-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

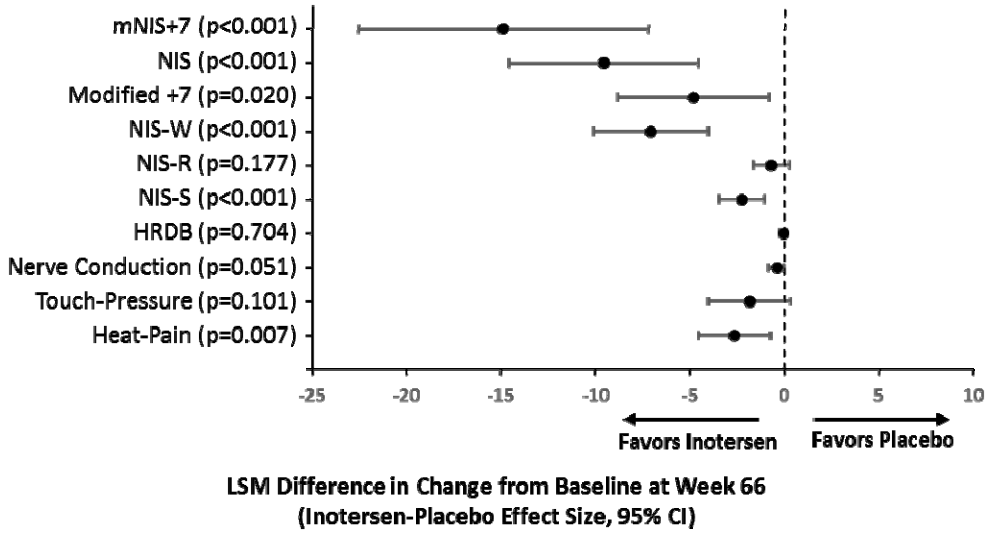
	mNIS+7		Norfolk-QOL-DN	
	Placebo (N=60)	Inotersen (N=112)	Placebo (N=60)	Inotersen (N=112)
Baseline				
n	60	112	59	111
Mean (SD)	74.75 (39.003)	79.16 (36.958)	48.68 (26.746)	48.22 (27.503)
Week 66 Change				
n	60	112	59	111
LSM (SE)	25.43 (3.225)	10.54 (2.397)	12.94 (2.840)	4.38 (2.175)
95% CI	19.11, 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

Quality of Life-Diabetic Neuropathy (QoL-DN)
Standard deviation (SD)
Least squares mean (LSM)

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

	mNIS+7			Norfolk QoL-DN		
		Change from Baseline Inotersen – Placebo			Change from Baseline Inotersen – Placebo	
Subgroup	n	LSM	P-value	n	LSM	P-value

	(Placebo, Inotersen)	Difference (SE)		(Placebo, Inotersen)	Difference (SE)	
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 (5.334)	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



Least squares mean (LSM)
Quality of Life-Diabetic Neuropathy (QoL-DN)
modified Neuropathy Impairment Score (mNIS)
NIS-W – sub-score for weakness
NIS-R – sub-score for muscle stretch reflexes
NIS-S – sub-score for clinical sensation
Heart Rate during Deep Breathing (HRDB)

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-point to 30-point increase from baseline (using the safety set), showed the inotersen 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 subject who had a change from baseline that was less than or equal to the threshold value. Subjects that terminate the treatment early irrespective of the reason or have missing week 66 data are considered as non-responders. Statistical significance in favour of inotersen was demonstrated at all thresholds beyond a 0-point change.

Paediatric population

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 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

Biotransformation

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 active substance is limited to less than 1% within the 24 hours post dose. Following subcutaneous administration, elimination half-life for inotersen is approximately 1 month.

Special populations

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

Elderly population

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

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.

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.

5.3 Preclinical safety data

Toxicology

Decreased platelet counts were observed in chronic toxicity studies in mice, rats and monkeys at 1.4 to 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 recommended therapeutic dose in all animal species tested and were accompanied by increases of various plasma cytokines/chemokines.

Genotoxicity/ carcinogenicity

Inotersen did not exhibit genotoxic potential in *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 toxicology

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

5 years.

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

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

1.5 mL solution in a clear Type 1 glass pre-filled syringe.

Tray with tear-off lid.

Pack sizes of 1 or 4 pre-filled syringes. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PLGB 51704/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01/01/2021
Date of latest renewal: 06/07/2023

10 DATE OF REVISION OF THE TEXT

08/01/2024