ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See Section 4.8 for how to report adverse reactions

1. NAME OF THE MEDICINAL PRODUCT

Tegsedi 284 mg solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 284 mg inotersen (as sodium).

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 treatment recommendations for platelet count

Platelet count x 10^9/L)	**Monitoring frequency**	**Dosing**
> 100	Every 2 weeks	Weekly dosing should be continued.
≥ 75 à < 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 reverse the platelet decline. Patients who discontinue therapy with inotersen due to platelet counts below 25 x 109/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 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/1.73m2 (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 dosing of 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.

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/1.73m^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 (see section 4.8). Platelet count should be monitored every 2 weeks during 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), neck stiffness or atypical severe headache.

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 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 inotersen. 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 inotersen and may be harmful to the mother and foetus.

Liver monitoring

Hepatic enzymes should be measured 4 months after initiation of treatment with inotersen and annually thereafter or more frequently as clinically indicated, in order to detect cases of hepatic impairment (see section 4.8).

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) 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 inotersen. This reaction typically resolves spontaneously after a few days of treatment.

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 section 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). Although the population PK analysis did not identify clinically relevant effects of some nephrotoxic medicines on the clearance of inotersen or on the potential for an effect on renal function, 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 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 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		

System Organ Class	Very Common	Common	Uncommon
	Nausea		
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	Pyrexia Chills Injection site reactions Peripheral oedema	Influenza like illness Peripheral swelling Injection site discolouration	
Injury, poisoning and procedural complications		Contusion	

Description of selected adverse reactions

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
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).

Glomerulonephritis / renal function decline
Patients should be monitored for signs of increased proteinuria and reduction in eGFR 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 (C_{max}, 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 the national reporting system listed in Annex V.

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 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.

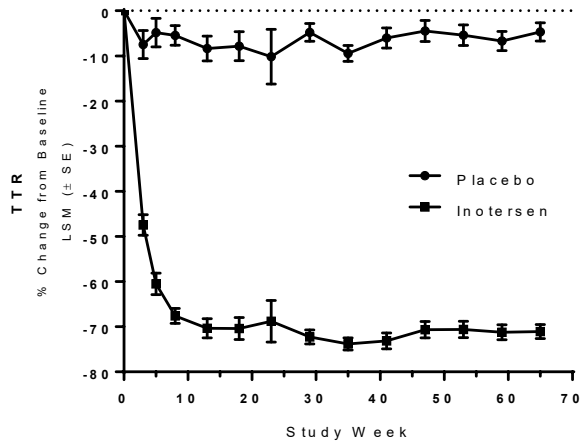


Figure 1 Percent Change from Baseline in Serum TTR Over Time

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 an 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.

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 Mean (SD)	 60 74,75 (39,003)	 112 79,165 (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) 15,85, 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 Inotersen – Placebo			Change from Baseline Inotersen – Placebo	
Subgroup	N (Placebo, Inotersen)	LSM Difference (SE)	P-value	n (Placebo, Inotersen)	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 (5,334)	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

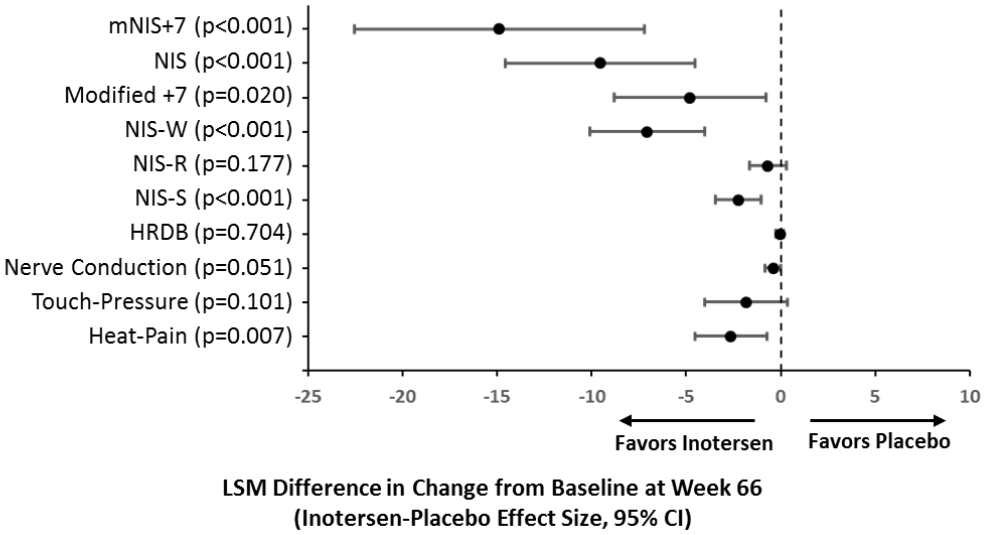


Figure 2 Difference in Least Squares Mean (LSM) Change from Baseline Between Treatment Groups in mNIS+7 and Components

A responder analysis of mNIS+7 using thresholds ranging from a 0- to 30-point increase from baseline (using the safety set), showed the 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 drug 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 SC 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 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.

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 and other 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.

7. MARKETING AUTHORISATION HOLDER

Akcea Therapeutics Ireland Ltd
St. James House,
72 Adelaide Road, Dublin 2
D02 Y017, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1296/001
EU/1/18/1296/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 July 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION]

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

ABF Pharmaceutical Services GmbH
Brunnerstraße 63/18-19
1230 Vienna
AUSTRIA

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Tegsedi in each Member State (MS), the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each MS where Tegsedi is marketed, all patients who are expected to been administered the products are provided with a patient alert card (wallet size), aiming at preventing and/or minimising the important identified risks of thrombocytopenia, glomerulonephritis, the important potential risk of ocular toxicity due to vitamin A deficiency, liver transplant rejection and reminding patients:

- To carry the card with them at all times during the treatment and up to 8 weeks following treatment discontinuation;
- The list of signs and symptoms of thrombocytopenia, glomerulonephritis, ocular toxicity due to vitamin A deficiency and liver transplant rejection, highlighting that these might be severe or life-threatening, and advising patients to call immediately their doctor or attend the emergency room if such signs and symptoms appear;
- To undergo all blood or urine tests as arranged by their doctor;
- To have a list of all other medicines they are using for any visit to a Health Care Professional (HCP);

In addition to a prompt to include the contact details of the patient's physician and a call for reporting, the patient card should also:

- Alert HCPs that the patient is taking Tegsedi, its indication and the key safety concerns;
- Advise HCPs that, due to the risks of thrombocytopenia and glomerulonephritis, patients should have their platelet count monitored at least every 2 weeks, and urine protein to creatinine ratio and estimated glomerular filtration rate monitored at least every 3 months or more frequently as clinically indicated, based on history of chronic kidney disease and/or renal amyloidosis;
- Advise HCPs that if the platelet count falls below 25 x 10^9/L, Tegsedi treatment should be permanently discontinued and corticosteroid therapy is recommended;
- Advise HCPs that the platelet count, UPCR and eGFR should be monitored for 8 weeks following discontinuation of treatment;
- Advise HCPs that if glomerulonephritis is confirmed, Tegsedi treatment should be permanently discontinued and early initiation of immunosuppressive therapy should be considered;
- Advise HCPs that 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. Patients with a prior liver transplant should be monitored for signs and symptoms of transplant rejection during treatment with Tegsedi. In these patients, liver function tests should be performed monthly;
- Advise HCPs that if patients develop ocular symptoms consistent with vitamin A deficiency, referral for ophthalmological assessment is recommended;
- Advise HCPs that discontinuation of Tegsedi should be considered in patients who develop liver transplant rejection during treatment.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tegsedi 284 mg solution for injection in pre-filled syringe
inotersen

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 284 mg inotersen (as sodium).

3. LIST OF EXCIPIENTS

Also contains: hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe
4 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only
Lift here and pull to open

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Following distribution to the patient, can be stored 6 weeks below 30°C. If not used, should be discarded.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Akcea Therapeutics Ireland Ltd
St. James House,
72 Adelaide Road, Dublin 2
D02 Y017, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1296/001
EU/1/18/1296/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tegsedi

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. IDENTIFIANT UNIQUE – DONNÉES LISIBLES PAR LES HUMAINS

PC :
SN :
NN :

PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
TRAY TEAR-OFF LID

1. NAME OF THE MEDICINAL PRODUCT

Tegsedi 284 mg solution for injection in pre-filled syringe
inotersen

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Akcea Therapeutics

3. EXPIRY DATE

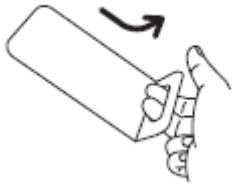
EXP

4. BATCH NUMBER

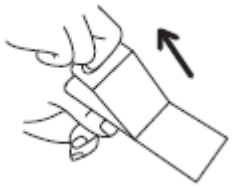
Lot

5. OTHER

Subcutaneous use



.
1. Bend and snap



2. Pull to open

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Tegsedi 284 mg injection
inotersen
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Tegsedi 284 mg solution for injection in pre-filled syringe
inotersen

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tegsedi is and what it is used for

Tegsedi contains the active substance inotersen. It is used to treat adults with hereditary transthyretin amyloidosis. Hereditary transthyretin amyloidosis is a genetic disease, which causes build-up of small fibres of a protein called transthyretin in the organs of your body stopping them from working properly. Tegsedi is used when the disease is causing symptoms of polyneuropathy (nerve damage).

The active substance in Tegsedi, inotersen, is a type of medicine called an antisense oligonucleotide inhibitor. It works by reducing production of transthyretin by the liver and so lowers the risk of fibres of transthyretin being deposited in body organs and causing symptoms.

2. What you need to know before you use Tegsedi

Do not use Tegsedi if:
- you are allergic to inotersen or any of the other ingredients of this medicine (listed in section 6).
- tests show you have excessively low numbers of platelets, the cells in your blood which stick together helping it clot.
- tests of kidney function or protein in the urine show signs of severe kidney problems.
- you have severe reduction in liver function (hepatic impairment)

Warnings and precautions

Before you begin treatment with Tegsedi, your doctor will measure your blood cells, liver function, kidney function, and protein levels in your urine. You will only be treated with Tegsedi if these are all at acceptable levels and your doctor will repeat these checks regularly during treatment.

Thrombocytopenia
Tegsedi may reduce cells in the blood responsible for clotting of the blood (platelets), which may result in a condition called thrombocytopenia (see section 4). When you do not have enough platelets, like in thrombocytopenia, your blood may not clot quickly enough to stop bleeding. This can lead to bruising as well as other more serious problems such as excessive bleeding and internal bleeding. Your doctor will check your blood for levels of platelets before treatment and regularly during treatment with Tegsedi. If you stop taking Tegsedi then your blood levels should be checked 8 weeks after discontinuation.

If you are taking any medicines that can lower platelet count or stop blood from clotting, for example acetylsalicylic acid, clopidogrel, warfarin, heparin, rivoraxaban and dabigatran, you must tell your doctor before you use Tegsedi.

You should see your doctor immediately if you have unexplained bruising or a rash of small patches of red appearing on the skin (called petechiae), bleeding from skin cuts that does not stop or oozes, bleeding from the gums or nose, blood in urine or stools, bleeding in the whites of your eyes. Call for immediate help if you have stiffness of the neck or an unusual and severe headache because these symptoms may be caused by bleeding in the brain.

Glomerulonephritis / kidney problems
Glomerulonephritis is a condition of your kidneys, where they do not work properly due to inflammation and kidney damage. Some patients treated with inotersen have developed this condition. Symptoms of glomerulonephritis are foaming urine, pink or brown coloured urine, blood in the urine, and passing less urine than usual.
Some patients treated with inotersen have also developed a decline in their kidney function without having had glomerulonephritis.
Your doctor will check your kidney function before treatment and regularly during treatment with Tegsedi. If you stop taking Tegsedi then your kidney function should be checked 8 weeks after discontinuation. If you develop glomerulonephritis, your doctor will treat you for this condition.

If you are using any medicines that damage the kidney or affect kidney function, for example sulfonamides, aldosterone antagonists, and some types of painkillers, you should tell your doctor.

Vitamin A deficiency
Tegsedi can lower your body's levels of vitamin A (also called retinol). You doctor will measure these, and if they are already low, this should be corrected and any symptoms resolved before you start treatment with Tegsedi. Symptoms of low vitamin A include:

- dry eyes, poor vision, decrease in night vision, hazy or cloudy vision

If you have problems with your sight or any other eye problems when you are using Tegsedi, you should speak to your doctor. Your doctor may refer you to an eye specialist for a check-up if it is necessary.

Your doctor will ask you to take a daily vitamin A supplement during treatment with Tegsedi.

Both excess and deficient levels of vitamin A can harm the development of your unborn child. Therefore women of child-bearing age should exclude any pregnancy, before treatment initiation with Tegsedi and should practise effective contraception (see section *"Pregnancy and breast-feeding"* below).

If you are planning to become pregnant you should stop taking inotersen including vitamin A supplementation and ensure that your vitamin A levels have returned to normal before conception is attempted.

If you have an unplanned pregnancy you should stop taking inotersen. Due to the prolonged activity of Tegsedi, however, your reduced vitamin A levels may persist. It is unknown if continuation of your vitamin A supplementation with 3000 IU per day will be harmful to your unborn child in the first trimester of your pregnancy, but this dose should not be exceeded. You should resume the vitamin A supplementation during your second and third trimesters of your pregnancy if your vitamin A levels have not yet returned to normal, because of the increased risk of vitamin A deficiency in the third trimester.

Liver Transplant Rejection
Talk to your doctor before using TEGSEDI if you have previously received a liver transplant. Cases of liver transplant rejection have been reported in patients being treated with Tegsedi. Your doctor will monitor you regularly for this during treatment with Tegsedi.

Children and adolescents
Tegsedi should not be used in children and adolescents under 18 years old.

Other medicines and Tegsedi
Tell your doctor or pharmacist if you are taking, have recently taken or might use any other medicines. It is important that you tell your doctor if you are already being treated with any of the following:

- Medicines to prevent blood clots or that lower the platelet numbers in your blood, e.g., acetylsalicylic acid, heparin, warfarin, clopidogrel, rivoraxaban and dabigatran.
- Any medicines that may alter your kidney function or may damage the kidneys, e.g., sulfonamides (used as an antibacterial), anilides (used to treat fever, aches and pains), aldosterone antagonists (used as a diuretic) and natural opium alkaloids and other opioids (used for treatment of pain).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before using this medicine.

Women of child-bearing age
Tegsedi will reduce the level of vitamin A in your body, which is important for normal foetal development during pregnancy. It is unknown if vitamin A supplementation can compensate for the risk of vitamin A deficiency that might affect your unborn child (see *"Warnings and precautions"* above). If you are a woman of child-bearing age, you should practise effective contraception and any pregnancy should be excluded before starting the treatment with Tegsedi.

Pregnancy
You should not use Tegsedi if you are pregnant, unless explicitly advised by your doctor. If you are of child-bearing age and intend to use Tegsedi, you should practise effective contraception.

Breast-feeding
Tegsedi may pass into breast milk. You should consult your doctor if you should either stop breast-feeding or stop the treatment with Tegsedi.

Driving and using machines

Use of Tegsedi has not been shown to affect ability to drive or use machinery.

3. How to use Tegsedi

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose of Tegsedi is one dose of 284 mg inotersen.

Doses should be administered once every week. All subsequent doses should be injected once weekly on the same day each week.

Route and method of administration

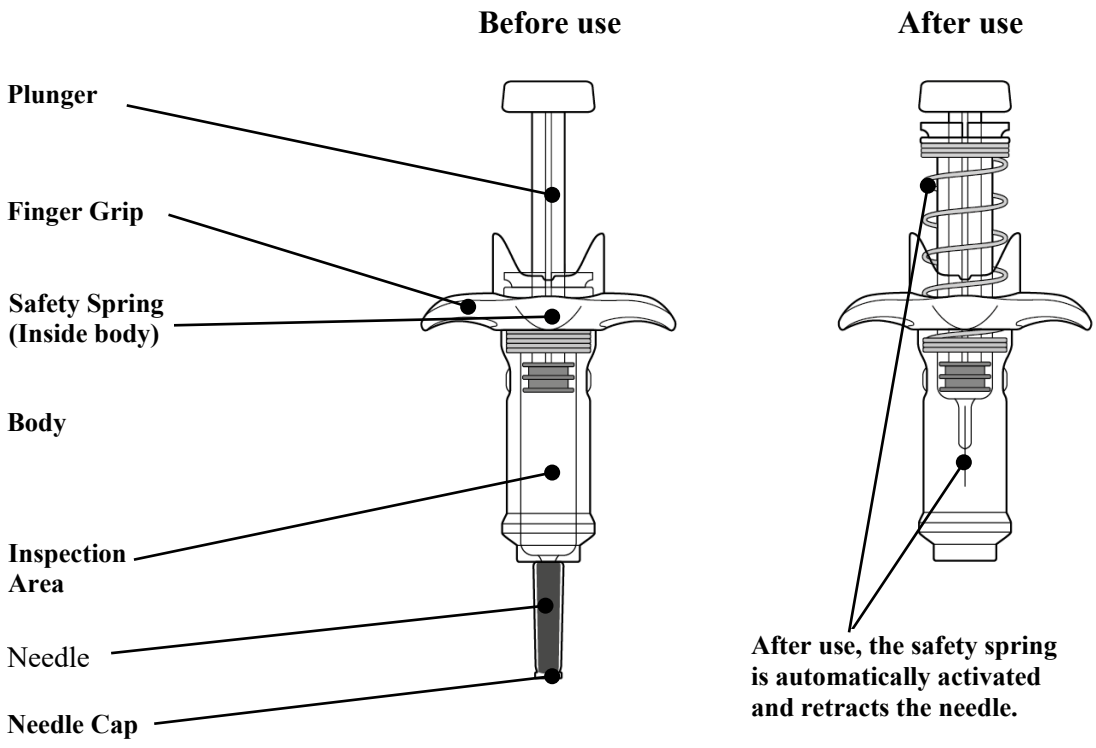
Tegsedi is for injection under the skin (subcutaneous use) only.

Instructions for use

Before using your pre-filled syringe, your doctor should show you or your caregiver how to use it the right way. If you or your caregiver have any questions, ask your doctor.

Read the Instructions for Use before you start using your pre-filled syringe and each time you get a repeat prescription. There may be new information.

Guide to parts



Each pre-filled syringe contains one dose and is for one-time use only.

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 the pre-filled syringe is dropped onto a hard surface or is damaged;
Do not freeze the pre-filled syringe;
If any of the above happens, throw away the pre-filled syringe in a puncture-resistant (sharps) container and use a new pre-filled syringe.

PREPARATION

1. Gather supplies

- 1 Pre-filled syringe from the refrigerator
- 1 Alcohol wipe (not supplied)
- 1 Gauze pad or cotton ball (not supplied)
- 1 Puncture-resistant (sharps) container (not supplied)

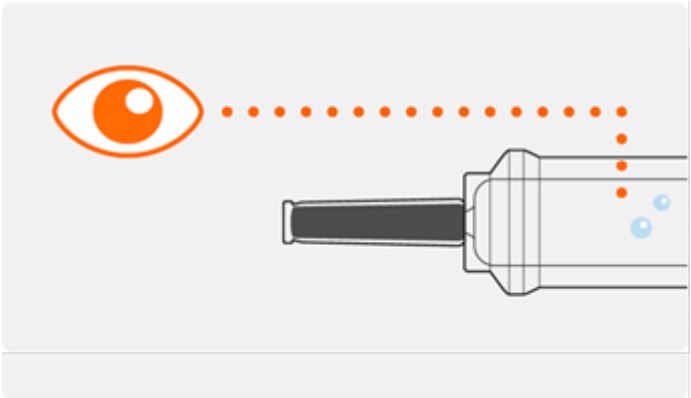
Do not inject the medicine until you have gathered the supplies listed.

2. Prepare to use your pre-filled syringe

- Remove the plastic tray from the carton and check the expiry date. Do not use if the expiry date has passed.
- Let the pre-filled syringe reach room temperature (20 °C to 25 °C) for 30 minutes before injecting it. **Do not** warm the pre-filled syringe in any other way. For example, **do not** warm in a microwave or hot water, or near other heat sources.
- Remove the pre-filled syringe from the tray by holding onto the syringe body.

Do not move the plunger.

3. Check medicine in the pre-filled syringe

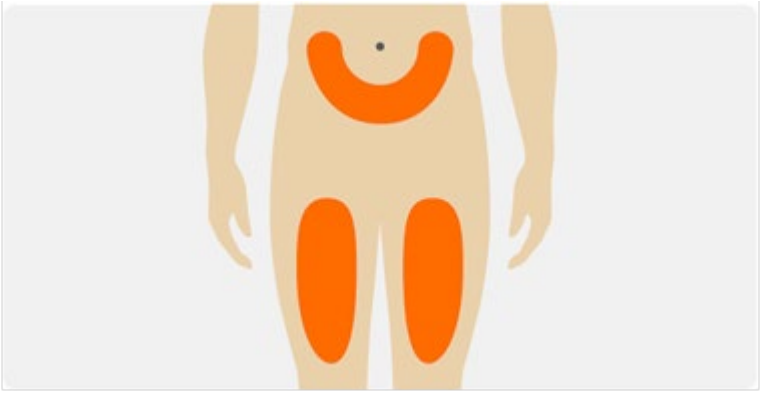


Look in the inspection area to check that the solution is clear and colourless or pale yellow. It is normal to see air bubbles in the solution. You do not need to do anything about it.

Do not use if the solution looks cloudy, discoloured, or has particles.

If the solution looks cloudy, discoloured or has particles, throw the pre-filled syringe away in a puncture resistant (sharps) container, and use a new pre-filled syringe.

4. Choose the injection site



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

The injection site may also be on the outer area of the upper arm if Tegsedi is administered by a caregiver.

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

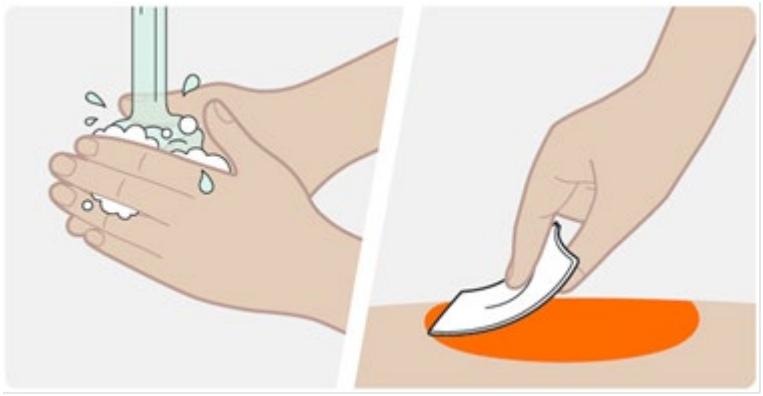
Do not inject into the same site each time.

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

Do not inject into tattoos, scars or damaged skin.

Do not inject through clothing.

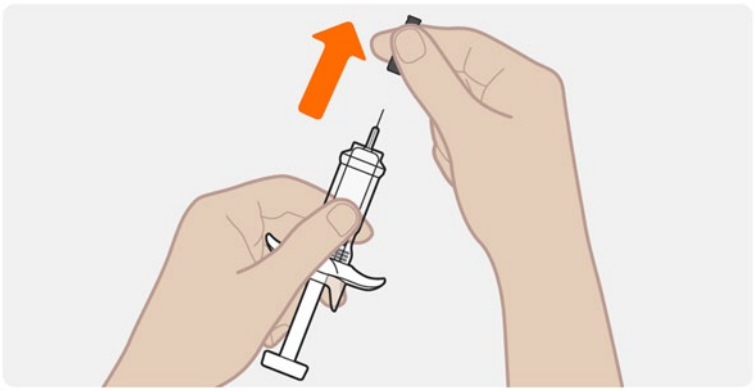
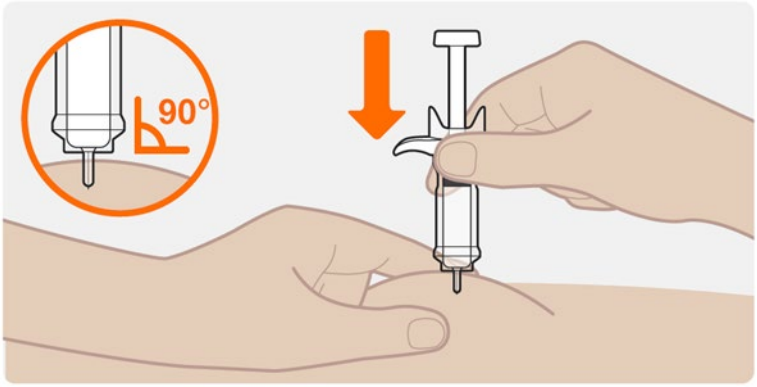
5. Clean the injection site



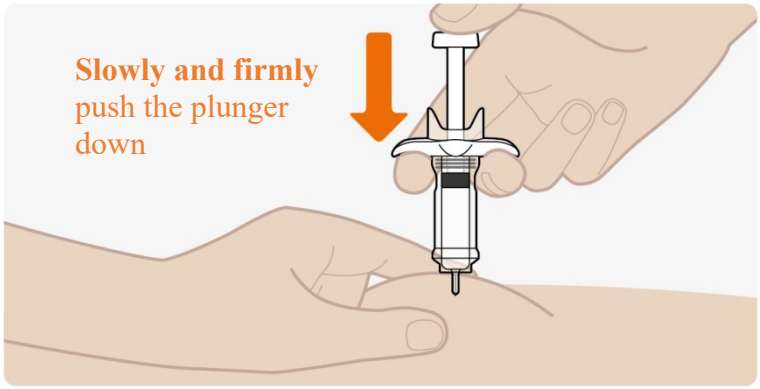
Wash your hands with soap and water.

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 pre-filled 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 pre-filled 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 pre-filled syringe. **Do not** put the needle cap back onto the pre-filled syringe.
7. Insert the needle	
	Hold the pre-filled 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 needle into the chosen injection site at a 90° angle until it is fully inserted. **Do not** hold the pre-filled 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.

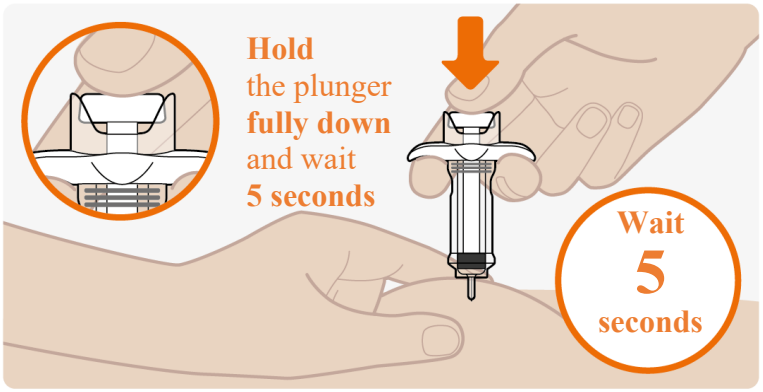
It is important to push the plunger all the way down.

Your pre-filled 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 stiff 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

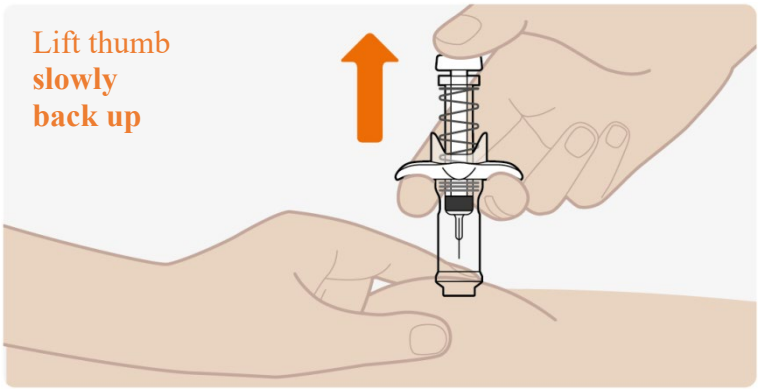


Push firmly on the plunger at the end of the injection. Hold the plunger fully down and wait for **5 seconds**. If you let go of the plunger too quickly, you may lose some of the medicine.

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 pre-filled 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.

Do not pull the plunger up by hand. Lift the whole pre-filled 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 pre-filled syringe

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

If you use more Tegsedi than you should

Contact your doctor or pharmacist, or go to a hospital emergency department immediately, even if you have no symptoms.

If you forget to use Tegsedi

If you miss your dose of Tegsedi, then you should have your next dose 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 given at the scheduled time.

Do not take a double dose to make up for a forgotten dose.

If you stop using Tegsedi

Do not stop using Tegsedi unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

If you get any of the following side effects, stop using Tegsedi and contact your doctor immediately:
- Symptoms that could indicate glomerulonephritis, (where your kidneys do not work properly), such as foaming urine, pink or brown coloured urine, blood in the urine, or passing less urine than usual.
- Symptoms that could indicate thrombocytopenia (where blood will not clot), such as unexplained bruising or a rash of small patches of red appearing on the skin (called petechiae), bleeding from skin cuts that does not stop or oozes, bleeding from the gums or nose, blood in urine or stools, or bleeding in the whites of your eyes.

Call for immediate help if you have stiffness of the neck or an unusual and severe headache because these symptoms may be caused by bleeding in the brain.

Other side effects

Very common (may affect more than 1 in 10 people)

- Reduction in red blood cells which can make the skin pale and cause weakness or breathlessness (anaemia)
- Headache
- Vomiting, or nausea (feeling sick)
- Increase in body temperature
- Feeling cold (chills) or shivering
- Injection site pain, redness, itching or bruising
- Swelling of the ankles, feet or fingers (peripheral oedema)

Common (may affect up to 1 in 10 people)

- An increase in the number of white blood cells called eosinophils in your blood (eosinophilia)
- Decreased appetite
- Feeling faint or dizzy, especially on standing up (low blood pressure, hypotension)
- Bruising
- Collection of blood within the tissues, that may look similar to severe bruising (haematoma)
- Itching
- Rash
- Kidney damage leading to poor kidney function or kidney failure
- Changes to your blood and urine test results (this may indicate infection or liver or kidney damage)
- Flu like symptoms, such as high temperature, aches and chills (influenza-like

illness)
- Injection site swelling or skin discolouration

Uncommon (may affect up to 1 in 100 people)
- Allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Annex V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tegsedi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton, tray and on the pre-filled syringe after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.
Tegsedi may be stored unrefrigerated for up to 6 weeks at a temperature below 30°C. If unrefrigerated and not used within 6 weeks then this medicine should be discarded.
Store in the original package in order to protect from light.

Do not use this medicine if you notice that the contents are cloudy or contains particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tegsedi contains

- The active substance is inotersen.
- Each pre-filled syringe contains 284 mg of inotersen.
- The other ingredients are water for injections, sodium hydroxide, and hydrochloric acid.

What Tegsedi looks like and contents of the pack

Tegsedi is a clear, colourless to pale yellow solution (pH 7.5 – 8.8) for injection (injection) in a pre-filled syringe.
Tegsedi is available in pack sizes of either 1 or 4 pre-filled syringes.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

Akcea Therapeutics Ireland Ltd
St. James House,
72 Adelaide Road, Dublin 2
D02 Y017, Ireland

Manufacturer

ABF Pharmaceutical Services GmbH
Brunnerstraße 63/18-19
1230 Vienna
Austria

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.