Summary of Risk Management Plan for Tegsedi (inotersen)

This is a summary of the risk management plan (RMP) for TEGSEDI. The RMP details important risks of TEGSEDI, how these risks can be minimised, and how more information will be obtained about TEGSEDI’s risks and uncertainties (missing information).

TEGSEDI’s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how TEGSEDI should be used.

This summary of the RMP for TEGSEDI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of TEGSEDI’s RMP.

I. The medicine and what it is used for

TEGSEDI is indicated for the treatment of adult patients with hereditary transthyretin amyloidosis with symptoms of polyneuropathy, Stage 1 or Stage 2 (see SmPC for the full indication). It contains inotersen as the active substance and it is given by subcutaneous (SC) injection.

Further information about the evaluation of TEGSEDI’s benefits can be found in TEGSEDI’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/tegsedi.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of TEGSEDI, together with measures to minimise such risks and the proposed studies for learning more about TEGSEDI’s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of TEGSEDI, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below. In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of TEGSEDI is not yet available, it is listed under ‘missing information’ below.
II.A List of important risks and missing information

Important risks of TEGSEDI are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TEGSEDI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

<table>
<thead>
<tr>
<th>List of important risks and missing information</th>
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<tr>
<td>Important identified risks</td>
</tr>
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<td>• Thrombocytopenia including a serious bleeding episode</td>
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<td>• Glomerulonephritis</td>
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<tr>
<td>Important potential risks</td>
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<td>• Liver transplant rejection</td>
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<td>• Use in pregnancy and lactation</td>
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<td>• Use in patients with hepatic impairment</td>
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<td>• Use in patients with renal impairment</td>
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<td>• Use in patients with NYHA classification 3 and 4 heart failure</td>
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<td>• Extended long-term safety</td>
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## II.B Summary of important risks

<table>
<thead>
<tr>
<th>Important Identified Risk – Thrombocytopenia including a serious bleeding episode</th>
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<td><strong>Evidence for linking the risk to the medicine</strong></td>
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<td><strong>Risk factors and risk groups</strong></td>
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<td><strong>Risk minimisation measures</strong></td>
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### Additional Pharmacovigilance Activities

**Additional Pharmacovigilance Activities:**
- **ISIS 420915-CS3:** An open-label extension study to assess the long-term safety and efficacy of TEGSEDI in patients with familial amyloid polyneuropathy.
- **TEG4001:** A prospective, non-interventional study to characterise the long-term safety of TEGSEDI in patients with hATTR-PN under real-world conditions.
- **TEG4002:** A retrospective, non-interventional, multi-centre study of TEGSEDI-treated patients to evaluate real-world adherence to, and effectiveness of, the recommendations for platelet monitoring, dose adjustment, and steroid initiation to manage risk of thrombocytopenia.

See section II.C of this summary for an overview of the post-authorisation development plan.

### Important Identified Risk - Glomerulonephritis

| Evidence for linking the risk to the medicine | Phase 3 pivotal trial – CS2  
|                                              | Open-label Extension Study - CS3 |
| Risk factors and risk groups                 | Patients with eGFR < 60 mL/min and those with P/C ratio > 2xULN |
| Risk minimisation measures                   | **Routine risk minimisation measures** |
|                                              | • SmPC section 4.8 |
|                                              | • PL section 4 |
|                                              | • Recommendations for renal monitoring in SmPC sections 4.2 and 4.8 and notification of renal function monitoring to patients in PL section 2. |
|                                              | • Recommended course of action if acute glomerulonephritis is confirmed or suspected in SmPC sections 4.2 and 4.4. |
|                                              | • Contraindication of use in patients with severe renal impairment (urine protein to creatinine ratio ≥ 113 mg/mol (1 g/g) and estimated glomerular filtration rate < 45 ml/min/1.73m²) in SmPC sections 4.2 and 4.3 and PL section 2. |
|                                              | • Caution advised for the use of TEGSEDI in patients deemed at higher risk of glomerulonephritis in SmPC section 4.4 and 4.5. |
|                                              | • Instructions for patients to notify their doctor if they are taking any medications that can damage the kidney or affect kidney function in PL section 2. |
|                                              | • Instructions for patients to notify their doctor immediately and stop taking TEGSEDI if they experience any signs or symptoms of glomerulonephritis in PL section 4. |
|                                              | • Legal status: Prescription only medication |

**Additional risk minimisation measures**
- Patient Alert Card
## Additional Pharmacovigilance Activities

**Additional pharmacovigilance activities:**
- ISIS 420915-CS3: An open-label extension study to assess the long-term safety and efficacy of TEGSEDI in patients with familial amyloid polyneuropathy
- TEG4001: A prospective, non-interventional study to characterise the long-term safety of TEGSEDI in patients with hATTR-PN under real-world conditions

See section II.C of this summary for an overview of the post-authorisation development plan.

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## Important Potential Risk - Ocular Toxicity due to vitamin A Deficiency

### Evidence for linking the risk to the medicine

One of the main functions of TTR is to bind to the RBP4-retinol complex and thereby prevent renal clearance of this complex. Therefore, reductions of plasma TTR levels are predicted to cause a subsequent decrease in plasma RBP4 levels. As expected, treatment with TEGSEDI in monkeys caused a time-dependent reduction in circulating RBP4 levels similar to the kinetics observed for TTR levels. There was about 60% reduction in plasma RBP4 levels in several independent monkey studies, but no sign of retinal toxicity through 9 months of treatment at doses up to 20 mg/kg/wk.

Studies CS2 and CS3

CS2 was a randomised controlled trial.

### Risk Factors and Risk Groups

Patients with a clinical history of vitamin A deficiency

### Risk Minimisation Measures

**Routine risk minimisation measures**
- SmPC section 4.4
- PL section 2
- Guidance on the correction of plasma vitamin A levels < LLN and resolution of ocular signs or symptoms of vitamin A deficiency prior to initiation of TEGSEDI treatment in SmPC section 4.4 and PL section 2.
- Recommendation for oral supplementation of vitamin A in SmPC section 4.4 and PL section 2.
- Guidance on the ocular symptoms that should trigger an ophthalmology referral in SmPC section 4.4.
- Instruction to notify the doctor of any problems with sight or with eyes in PL section 2.
- Legal status: Prescription only medication

**Additional risk minimisation measures**
- Patient Alert Card

### Additional Pharmacovigilance Activities

**Additional pharmacovigilance activities:**
- ISIS 420915-CS3: An open-label extension study to assess the long-term safety and efficacy of TEGSEDI in patients with familial amyloid polyneuropathy
- TEG4001: A prospective, non-interventional study to characterise the long-term safety of TEGSEDI in patients with hATTR-PN under real-world conditions

See section II.C of this summary for an overview of the post-authorisation development plan.
### Important Potential Risk – Liver Transplant Rejection

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Expanded access programme (CS5) and spontaneous source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>Use in Patients with prior or anticipated liver transplant</td>
</tr>
<tr>
<td>Risk minimisation measures</td>
<td><strong>Routine risk minimisation measures.</strong></td>
</tr>
<tr>
<td></td>
<td>• SmPC section 4.4</td>
</tr>
<tr>
<td></td>
<td>• PL section 2</td>
</tr>
<tr>
<td></td>
<td>• Recommendation to discontinue TEGSEDI dosing in patients undergoing liver transplant rejection in SmPC section 4.2 and to consider discontinuation of TEGSEDI in patients who develop liver transplant rejection during treatment in SmPC section 4.4.</td>
</tr>
<tr>
<td></td>
<td>• Instruction to monitor patients for signs and symptoms of liver transplant rejection during treatment with TEGSEDI in SmPC section 4.4.</td>
</tr>
<tr>
<td></td>
<td>• Instruction to perform liver function tests monthly in patients with a prior liver transplant in SmPC section 4.4.</td>
</tr>
<tr>
<td></td>
<td>• Instruction for patients to notify their doctor if they have previously received a liver transplant in PL section 2.</td>
</tr>
<tr>
<td></td>
<td>• Legal status: Prescription only medication</td>
</tr>
</tbody>
</table>

**Additional risk minimisation measures**

- Patient alert card

**Additional pharmacovigilance activities:**

- TEG4001: A prospective, non-interventional study to characterise the long-term safety of TEGSEDI in patients with hATTR-PN under real-world conditions

See section II.C of this summary for an overview of the post-authorisation development plan.

### Missing Information – Use in Pregnancy and Lactation

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th><strong>Routine risk minimisation measures</strong></th>
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<tbody>
<tr>
<td></td>
<td>• SmPC sections 4.4 and 4.6</td>
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<tr>
<td></td>
<td>• PL section 2</td>
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<tr>
<td></td>
<td>• Recommendation that pregnancy should be excluded prior to initiation of treatment, that women of child-bearing potential should practice effective contraception during treatment and details of actions that should be taken should a woman intend to become pregnant or should an unplanned pregnancy occur during TEGSEDI treatment in SmPC sections 4.4 and 4.6 and PL section 2.</td>
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<tr>
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<td>• Recommendation that a benefit assessment should be undertaken to determine whether breastfeeding or TEGSEDI therapy is discontinued in SmPC section 4.6 and PL section 2.</td>
</tr>
<tr>
<td></td>
<td>• Legal status: Prescription only medication</td>
</tr>
</tbody>
</table>

**Additional risk minimisation measures**

- None
### Additional pharmacovigilance activities

- **TEG4005**: Pregnancy Surveillance Program of Women and Infants Exposed to TEGSEDI During Pregnancy

  See section II.C of this summary for an overview of the post-authorisation development plan.

### Missing Information – Use in Patients with Hepatic Impairment

#### Risk minimisation measures

- **Routine risk minimisation measures**
  - SmPC section 5.2
  - Contraindication of use in patients with severe hepatic impairment in SmPC sections 4.2 and 4.3 and PL section 2.
  - Recommendation regarding dosing in patients with mild and moderate hepatic impairment in SmPC section 4.2.
  - Recommendation for liver function monitoring in SmPC section 4.4 and notification of monitoring to patients in PL section 2.
  - Legal status: Prescription only medication

#### Additional risk minimisation measures

- None

### Additional pharmacovigilance activities

- **TEG4001**: A prospective, non-interventional study to characterise the long-term safety of TEGSEDI in patients with hATTR-PN under real-world conditions

  See section II.C of this summary for an overview of the post-authorisation development plan.

### Missing Information – Use in Patients with Renal Impairment

#### Risk minimisation measures

- **Routine risk minimisation measures**
  - SmPC section 5.2
  - Contraindication of use in patients with severe renal impairment (urine protein to creatinine ratio ≥ 113 mg/mol (1 g/g) and estimated glomerular filtration rate < 45 ml/min/1.73m²) in SmPC sections 4.2 and 4.3 and PL section 2.
  - Recommendation regarding dosing in patients with mild and moderate renal impairment in SmPC section 4.2.
  - Recommendation for renal function monitoring in SmPC sections 4.4 and 4.8 and notification of renal function monitoring to patients in PL section 2.
  - Caution advised for concomitant use with nephrotoxic medicinal products or other products that may impair renal function in section SmPC sections 4.4 and 4.5.
  - Instructions for patients to notify their doctor if they are taking any medications that can damage the kidney or affect kidney function in PL section 2.
  - Legal status: Prescription only medication

#### Additional risk minimisation measures

- None
## Additional pharmacovigilance activities

**Additional pharmacovigilance activities:**
- TEG4001: A prospective, non-interventional study to characterise the long-term safety of TEGSEDI in patients with hATTR-PN under real-world conditions

See section II.C of this summary for an overview of the post-authorisation development plan.

### Missing Information – Use in Patients with NYHA Classification 3 and 4 Heart Failure

<table>
<thead>
<tr>
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See section II.C of this summary for an overview of the post-authorisation development plan.

### Missing Information – Extended Long-term Safety

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See section II.C of this summary for an overview of the post-authorisation development plan.

## II.C Post-authorisation development plan

### II.C.1 Studies which are conditions of the marketing authorisation

None.

### II.C.2 Other studies in post-authorisation development plan

**Study ISIS 420915-CS3**

**Study short name and title:**

CS3 – An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)

**Purpose of the study:**
The primary objective of the study is:

- To evaluate the safety and tolerability of extended dosing with TEGSEDI in patients with FAP

**Study TEG4001**

**Study short name and title:**

TEG4001 - A Prospective, Non-interventional, Long-term, Multinational Cohort Safety Study of Patients with Hereditary Transthyretin Amyloidosis with Polyneuropathy (hATTR-PN)

**Purpose of the study:**

The overarching goal of this study is to further characterise the long-term safety of TEGSEDI in patients with hATTR-PN under real-world conditions.

**The main objectives are:**

- To determine the incidence of thrombocytopenia in patients with hATTR-PN treated with TEGSEDI (TEGSEDI-exposed cohort)
- To compare relative rates of thrombocytopenia in hATTR-PN patients treated with TEGSEDI (TEGSEDI exposed) to hATTR-PN patients unexposed to TEGSEDI (TEGSEDI-unexposed)
- To describe the incidence of the following AESI in patients treated with TEGSEDI (TEGSEDI-exposed cohort) and to compare incidence in a cohort of patients unexposed to TEGSEDI with hATTR-PN (TEGSEDI-unexposed cohorts):
  - severe thrombocytopenia (platelet counts <25 x 10^9/L and separately, <50 x 10^9/L)
  - serious and non-serious bleeding events
  - glomerulonephritis
  - composite of stroke and/or cervicocephalic arterial dissection
  - central nervous system vasculitis
  - ocular toxicity due to vitamin A deficiency
- To describe the following in TEGSEDI-exposed and TEGSEDI-unexposed patients:
  - longitudinal patterns in platelet counts
  - time to onset of AESI (severe thrombocytopenia as described above, serious and non-serious bleeding events, glomerulonephritis, the composite of stroke and/or cervicocephalic arterial dissection, CNS vasculitis, and ocular toxicity due to vitamin A deficiency)
  - longitudinal patterns in estimated glomerular filtration rate (eGFR)
  - incidence and severity of renal toxicity/renal impairment
  - incidence and severity of hepatic abnormalities (hepatotoxicity/hepatic impairment)
  - longitudinal patterns in vitamin A levels
  - time to death
- To describe real-world incidence of all serious and non-serious adverse events (AEs), including overall AESI, in the following patient subgroups for both TEGSEDI-exposed and TEGSEDI-unexposed patients:
• patients with renal impairment
• patients with hepatic impairment
• patients who are pregnant or breastfeeding
• patients with NYHA Classification 3 and 4 heart failure
• patients who have undergone a liver transplant

• To describe TEGSEDI treatment discontinuations by reason for discontinuation
• To assess the receipt and use of the patient alert card

Study TEG4002

Study short name and title:
TEG4002 - A Retrospective, Non-interventional, Multi-centre Study of TEGSEDI-treated Patients to Evaluate Real-world Adherence to, and Effectiveness of, the Recommendations for Platelet Monitoring, Dose Adjustment, and Steroid Initiation to Manage Risk of Thrombocytopenia

Purpose of the study:
One of the important identified risks for TEGSEDI is thrombocytopenia, including a serious bleeding episode. In the post-authorisation setting, to mitigate the risk of thrombocytopenia through early detection, the SmPC recommends platelet monitoring every two weeks if the platelet count is greater than 100 x 10^9/L, and every week if the platelet count is 75 x 10^9/L to <100 x 10^9/L. The recommended frequency of platelet monitoring increases as the platelet count falls, to daily counts when the count is <25 x 10^9/L, with recommendations for dosing adjustment and, if applicable, treatment with steroids. Additionally, a patient alert card has been included as an additional risk minimisation measure in the post-authorisation setting. Top-line messages included in the patient alert card identify that the patient has been treated with TEGSEDI, which may result in thrombocytopenia including risk of a serious bleeding episode and includes information to help patients recognise warning signs and symptoms of low platelet count and serious bleeding.

The primary objective of the study is:
• To evaluate real-world adherence to, and effectiveness of, the recommended schedule for platelet monitoring, dose adjustment, and initiation of steroids for platelet recovery.

The secondary objectives of the study are:
• To evaluate real-world thrombocytopenia-related outcomes (e.g., incidence rates of thrombocytopenia and serious bleeding events associated with thrombocytopenia) in patients who receive TEGSEDI based on level(s) of adherence with recommendations for platelet monitoring and TEGSEDI dose adjustment per the SmPC
• To evaluate potential predictors of adherence with recommendations for platelet monitoring, TEGSEDI dose adjustment, and initiation of steroids for platelet recovery per the SmPC in patients who receive TEGSEDI

Study TEG4005

Study short name and title:
TEG4005: Pregnancy Surveillance Program of Women and Infants Exposed to TEGSEDI During Pregnancy

Purpose of the study:

Due to the lack of data reported on TEGSEDI exposure in human pregnancy, the background risk of major congenital malformations and miscarriage for the indicated population is unknown. As such, there are no data to assess drug-associated risks of birth defects, miscarriage, or adverse maternal or fetal outcomes. In order to better describe the safety profile of TEGSEDI when used during pregnancy, Akcea is conducting a pregnancy surveillance programme to collect and evaluate the effect of TEGSEDI on maternal pregnancy complications and outcomes, and on the health of infants exposed during pregnancy. The lack of data on human pregnancy exposures to TEGSEDI makes such a study an essential component of the ongoing programme of pharmacoepidemiological studies on the safety of this product.

The objectives of this pregnancy surveillance programme are to:

- Estimate the frequency of selected pregnancy and fetal/neonatal outcomes through 1 year of age in women who were exposed to at least 1 dose of TEGSEDI (Cohort 1) within 25 weeks prior to conception or during pregnancy, with the exposure window of interest for major congenital malformations being the first trimester, and in the unexposed cohort of pregnant women (Cohort 2) who have a diagnosis of hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN)
  - pregnancy outcomes include live births, spontaneous abortions, stillbirths, elective abortions, preterm birth
  - fetal/neonatal outcomes include major and minor congenital malformations, small for gestational age, failure to thrive, and postnatal development

- Estimate the frequency of selected pregnancy complications in women who were exposed to TEGSEDI (Cohort 1) within 25 weeks prior to conception or during pregnancy and in the unexposed cohort of pregnant women (Cohort 2) who have a diagnosis of hATTR-PN.