EU Risk Management Plan for Attrogy 250 mg film-coated tablets (diflunisal)

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 25 July 2025

Date of final sign-off: 28 July 2025

Rationale for submitting an updated RMP: Day 180 outstanding issues – Concerns regarding RMP

Summary of significant changes in this RMP: Part VI Public Summary amended as per CHMP and PRAC request. Approved indication and ATC code included post CHMP opinion

Other RMP versions under evaluation:

RMP Version number: N/A

Submitted on: N/A

Procedure number: N/A

Details of the currently approved RMP:

Version number: N/A

Approved with procedure: N/A

Date of approval (opinion date): N/A

QPPV name: Sari Öbrink

QPPV signature:

Table of content

Part I: Product Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Diflunisal
Pharmacotherapeutic group(s) (ATC Code)	NO2BA11
Marketing Authorisation Applicant	Purpose Pharma International AB
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Attrogy 250 mg film-coated tablets (abbreviated in this document to "Attrogy")
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Other nervous system drugs
	Summary of mode of action: Diflunisal acts by binding to and stabilising transthyretin (TTR), a thyroxine transport protein, in its tetramer form, preventing formation of amyloid plaques in individuals with hereditary transthyretin amyloid (ATTRv) amyloidosis, a lethal, autosomal dominant genetic disease. ATTRv amyloidosis is a gain-of-toxic-function protein mis-folding disease in which variant (mutated) TTR assembles into amyloid fibrils in extracellular spaces, leading to systemic organ dysfunction.
	Important information about its composition: N/A
Hyperlink to the Product Information	*Summary of Product Characteristics (SmPC)* Attrogy 250 mg film-coated tablets *Package Leaflet* Attrogy 250 mg film-coated tablets
Indication(s) in the EEA	Current: Attrogy is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.
	Proposed (if applicable): N/A
Dosage in the EEA	Current: 250 mg twice daily
	Proposed (if applicable): N/A
	Current (if applicable): film-coated tablet, 250 mg

Pharmaceutical form(s) and strengths	Proposed (if applicable): N/A
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication

Hereditary transthyretin amyloid amyloidosis (hATTR or ATTRv amyloidosis) is a rare, lethal, autosomal dominant genetic disease. Transthyretin (TTR) is a thyroxine transport protein predominantly produced by the liver and is present in all humans. The most common disease-causing mutation of the TTR gene is the V30M variant.

ATTRv amyloidosis is a gain-of-toxic-function protein mis-folding disease in which variant (mutated) TTR assembles into amyloid fibrils in extracellular spaces, leading to systemic organ dysfunction. TTR exists in plasma as a noncovalent, homotetramer (a dimer of dimers) presenting two identical binding sites located in a channel formed by the dimer−dimer interface and crossing the protein molecule. In this form the molecule is stable, the formation of amyloid is dependent on the dissociation of natively folded TTR tetramers into monomers.

The clinical presentation of ATTRv amyloidosis may vary depending on which disease-causing mutations are present. However, progressive polyneuropathy is a hallmark feature, and the disease is also known by the name of familial amyloid polyneuropathy (FAP or ATTR-FAP), although naming conventions have been revised several times over the last decade. In this document, the acronym ATTR-FAP will be used when referring to patients with ATTRv amyloidosis polyneuropathy.

Incidence: Incidence data are difficult to find in the literature and prevalence (see below) is a more appropriate tool to estimate the size of the problem.

Prevalence: Only a small number of publications providing data on the prevalence of transthyretin amyloid amyloidosis have been published. However, within these few publications (Parman Y2016; Schmidt HH2018; Auer-Grumbach M2020; Pozsonyi Z2021) there are prevalence estimates (covering all forms of ATTR amyloidosis, including wild-type) from numerous EU countries (Portugal, Sweden, Spain, Cyprus, Italy, France, Bulgaria, Austria, Hungary, The Netherlands and Germany). Detailed analysis of the data in these publications suggests the following:

- There are approximately 17,000 cases in the 11 EU countries listed above.
- This corresponds to approximately 0.5 per 10,000 in the general population.

There is wide variation among countries. Portugal (about 7,500 cases corresponding to a national prevalence of 7.3 per 10,000) and Sweden (about 7,000 cases corresponding to a national prevalence of 6.6 per 10,000) account for 85% of all cases.

The main existing treatment options

Current treatment options for ATTR-FAP include liver transplant and pharmacological treatments.

Liver transplant

Prior to the pharmacotherapy era, orthotopic liver transplant was the standard of care for patients with ATTR-FAP. A 20-year analysis of survival data from the Familial Amyloidotic Polyneuropathy World Transplant Registry of 2,044 liver transplant patients reported a 20-year survival rate of 55.3% after treatment.

Whereas liver transplant removes the main source of mutated TTR, it does not prevent progression of cardiac disease because the wild-type TTR may continue to further expand existing amyloid deposits in the heart. Therefore, continued scrutiny of the cardiac system is warranted, as some patients will develop atrioventricular blocks or infiltrative cardiomyopathy several years or decades later. A combined heart and liver transplant may be recommended in selected patients with non-V30M mutations and cardiomyopathy. However, ocular and central nervous system involvements often progress and/or appear after liver transplant due to the local synthesis of mutated TTR in retinal epithelium and choroid plexus (Adams D2016).

Pharmacological treatments

Tafamidis (Vyndaqel)

Tafamidis, introduced in 2011, binds with negative cooperativity to the two thyroxine binding sites on the native tetrameric form of transthyretin, preventing dissociation into monomers. The compound stabilises both the wild-type TTR tetramer and the tetramers of 14 TTR variants tested clinically after once-daily dosing. Tafamidis also stabilised the TTR tetramer for 25 variants tested *ex vivo* (Vyndaqel SmPC).

The approved indications are:

- "Treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment" (20 mg strength).
- "Treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)" (61 mg strength).

Inotersen (Tegsedi)

Inotersen, approved in July 2018, is a 2′-O-2-methoxyethyl phosphorothioate antisense oligonucleotide inhibitor of human transthyretin production. The selective binding of inotersen to the TTR messenger ribonucleic acid (RNA) causes the degradation of both mutant and wild-type 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 (Tegsedi SmPC).

The authorised indication is the "treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)".

Inotersen is presented as a solution for injection and is self-administered once weekly. It is recommended that patients use oral vitamin A supplementation (3,000 IE/day) when under treatment with inotersen. Thrombocytopenia is common.

Patisiran (Onpattro)

Patisiran, approved in August 2018, is a double-stranded small interfering ribonucleic acid that specifically targets a genetically conserved sequence in the 3' untranslated region of all mutant and wild-type TTR mRNA. Patisiran is formulated as lipid nanoparticles to deliver the siRNA to hepatocytes, the primary source of TTR protein in the circulation. Through a natural process called RNA interference, patisiran causes the catalytic degradation of TTR mRNA in the liver, resulting in a reduction of serum TTR protein (Onpattro SmPC).

The authorised indication is the "treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy".

Patisiran is presented as a solution for infusion and is administered once every 3 weeks by healthcare professionals. Again, supplemental vitamin A is recommended. In addition, patients require premedication with intravenous corticosteroid, H_1 and H_2 blockers plus oral paracetamol to reduce the risk of infusion-related reactions.

Vutrisiran (Amvuttra)

Vutrisiran, approved in September 2022, is a siRNA which targets variant and wild-type TTR mRNA. It is covalently linked to a ligand containing three N-acetylgalactosamine residues to enable delivery of the siRNA to hepatocytes. It causes the catalytic degradation of TTR mRNA in the liver, resulting in the reduction of variant and wild-type serum TTR protein levels.

The authorised indication is the "treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy" (Amvuttra SmPC).

Vutrisiran is presented as a solution for subcutaneous injection and is administered every three months. Vutrisiran should be administered by a healthcare professional. As treatment with vutrisiran reduces levels of retinol, patients who are being treated with vutrisiran should be administered 2,500-3,000 IE vitamin A per day to reduce the risk of ocular side-effects.

Important potential risk with vutrisiran are clinical consequences of vitamin A deficiency including delayed symptoms, and hypersensitivity reactions.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

The main clinical manifestations of ATTR-FAP are progressive peripheral sensorimotor and autonomic neuropathy (Planté-Bordeneuve V2011). Non-specific and symmetrical numbness, pain, and temperature sensitivity typically begins in the lower extremities, progressing distal to proximal. Motor neuropathy follows within a few years, which affects ambulatory status (Conduluci A, Theaudin M, Schwotzer R et al. Management of transthyretin amyloidosis. Swiss Med Wkly. 2021; 20; 151:w30053.
Coutinho P,1980; Sekijima Y2021; Planté-Bordeneuve V2011). Ambulatory status can range from needing support when walking to requiring the patient to use a wheelchair or become bedridden.

Life-threatening autonomic dysfunction develops in many patients, affecting the cardiocirculatory, gastrointestinal and genitourinary systems. Symptoms include orthostatic hypotension, which can lead to dizziness and frequent falls. This could result in fractures with subsequently hospital omissions.

Gastrointestinal symptoms include diarrhoea, severe constipation, alternating diarrhoea / constipation, vomiting and gastroparesis, all leading to progressive weight loss. Urinary symptoms, faecal incontinence and, in men, erectile dysfunction may be present (Planté-Bordeneuve V2011).

Amyloid deposits in the kidney are common and can result in microalbuminuria with progression to renal failure in a subset of patients. Renal failure typically results in need for dialysis or kidney transplants. Symptoms of chronic kidney disease may include lower extremity oedema, anaemia, fatigue and weakness, and decrease in appetite.

Cardiac involvement has been estimated to occur in 80% of cases of ATTR-FAP, and some cases have an exclusively or predominantly cardiac phenotype (Planté-Bordeneuve V2011). Mutant TTR amyloid fibrils infiltrate the myocardium, with resultant diastolic dysfunction progressing to restrictive cardiomyopathy and heart failure (Castaño A2015). Conduction abnormalities and arrhythmias are also common, and many patients require pacemaker and/or defibrillator insertion.

Given the severity of ATTR-FAP, there is a significant impact on patients' and caregivers' quality of life (Gertz MA2017; Stewart M2018). Caregivers have moderate to high levels of fatigue and spend a significant amount of time caring for patients. ATTR-FAP is associated with a substantial disruption in employment rates and work productivity. There is also a large mental health burden on both caregivers and patients, and an increased risk of depression and suicidal ideation and behaviour could not be excluded.

The "First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy" (Adams D2016) states that:

- "Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a highly debilitating and irreversible neurological disorder presenting symptoms of progressive sensorimotor and autonomic neuropathy."
- "TTR-FAP usually proves fatal within 7–12 years from the onset of symptoms, most often due to cardiac dysfunction, infection, or cachexia."

A more recent review by Gertz MAet al (2019) includes the following:

- "Hereditary transthyretin-mediated (hATTR) amyloidosis, caused by mis-folding of the TTR protein, is a progressive, degenerative, multisystemic, life-threatening disease."

The range of clinical problems associated with ATTR amyloidosis (taken from the review by Gertz MAet al, 2019) is summarised below.

Table SI.1 Clinical features of ATTR amyloidosis

Neuropathy	• Progressive symmetric peripheral sensorimotor neuropathy
Carpal tunnel syndrome	• Bilateral carpal tunnel syndrome (especially if family history)
Autonomic neuropathy	• Orthostatic hypotension • Erectile dysfunction • Recurrent urinary tract infection (due to urinary retention) • Sexual dysfunction • Sweating abnormalities
Cardiovascular manifestations	• Irregular heartbeat (atrial fibrillation most common)

	• Conduction blocks (including bundle branch blocks) • Congestive heart failure (including shortness of breath, generalised fatigue, and peripheral oedema) • Ventricular wall thickening with preserved ejection fraction and absence of left ventricular dilation • Cardiomyopathy • Mild regurgitation
Gastrointestinal manifestations	• Nausea and vomiting • Early satiety • Chronic diarrhoea • Severe constipation • Diarrhoea / constipation • Unintentional weight loss
Nephropathy	• Albuminuria • Mild azotaemia • Protein in urine • Renal failure
Ocular Manifestations	• Dark floaters • Glaucoma • Abnormal blood vessels in eye • Pupillary abnormalities
Other	• Lumbar spinal stenosis; spontaneous distal biceps tendon rupture

It is clear, therefore, that ATTR amyloidosis is a life-threatening condition which is also associated with serious and chronic debilitation.

Important co-morbidities

ATTR-FAP is a hereditary disease with progressive clinical manifestations if not diagnosed and treated. Important co-morbidities expected would therefore be clinical manifestations of the disease if not treated, including motor neuropathy deficiencies affecting ambulatory status, autonomic dysfunction affecting the cardiocirculatory, gastrointestinal and genitourinary systems (including cardiomyopathy, heart failure, arrhythmias, and renal failure).

The organ systems affected or initially affected depends on the type of mutation that is the cause of the disease.

Please also refer to section “Natural history of the indicated condition in the untreated population, including mortality and morbidity”.

Part II: Module SII - Non-clinical part of the safety specification

The Applicant has not performed any new non-clinical studies with diflunisal, and no such studies are planned.

The findings from the non-clinical studies supporting the initial European marketing authorisation application (MAA) for diflunisal (Donobid) are presented and discussed in Module 2.4 Non-clinical Overview of the present application. Additionally, a comprehensive review of the published scientific literature was performed. Taken together, diflunisal has a well-established non-clinical safety profile, and many non-clinical findings are representative of NSAIDs as a class. The findings are appropriately reflected in sections 4.3, 4.4, 4.5, 4.6, and 5.3 of the proposed SmPC for Attrogy.

Part II: Module SIII - Clinical trial exposure

Within the indication of ATTR-FAP, detailed information from one clinical trial (NCT00294671; EudraCT 2006-001066-16) is provided with the MAA linked to this RMP, please see below.

Title: THE EFFECT OF DIFLUNISAL (IND 68092) ON FAMILIAL AMYLOIDOSIS: A randomized, double-blind, placebo-controlled, international multi-center trial of diflunisal on neurologic disease progression in 200 familial amyloid subjects

Principal Investigator: John L. Berk, MD (Boston University, MA, USA)

Study drug: Dolobid (diflunisal) 250 mg tablets (NDC 0006-0675-61)

Study objectives: Primary objective: To determine whether diflunisal inhibits (peripheral and autonomic neuropathic) disease progression in patients with familial amyloid polyneuropathy (FAP).

Inclusion criteria: Biopsy proven amyloid deposition. Genotyping of variant TTR. Signs of peripheral neuropathy - detectable by a neurologist (performance status ≤3) or autonomic neuropathy detectable by a study investigator. Age >18 and <75 years. Negative β-HCG testing and contraception for sexually active women of child-bearing potential.

Exposure to diflunisal for patients in the trial is summarised in the tables below.

The dosage of diflunisal was 250 mg twice daily in all patients.

Table SIII.1: Duration of diflunisal exposure

Duration	Patients	Patient-days
<1 m	1	5
1 to <3 m	3	124
3 to <6 m	5	792
6 to <12 m	4	989
≥12 m	51	34 079
Total	64	35 989

Table SIII.2: Diflunisal exposure by age group and gender

Age Group	Patients		Patient-days	
	M	F	M	F
Adults (18 to 64 years)	22	13	11 248	7 622
Elderly people				
65 to 74 years	20	7	11 493	4 853
75 to 84 years	1	1	42	731
Total	43	21	22 783	13 206

Table SIII.3: Diflunisal exposure by ethnic origin

Ethnic origin	Patients	Patient-days
Asian	8	4 843
Black	1	106
White	52	29 905
Mediterranean	3	1 135
Total	64	35 989

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The complete exclusion criteria in the pivotal trial for the indication treatment of ATTR-FAP described in Module SIII (NCT00294671; EudraCT 2006-001066-16) according to the last approved version of the clinical study protocol (version 5, 17 July 2011) were:

1. Concomitant use of non-study non-steroidal anti-inflammatory drugs (NSAIDs), other than low-dose aspirin
2. Other causes of sensorimotor polyneuropathy
    a. Vitamin B12 deficiency
    b. HIV patients on anti-retroviral drugs
    c. Diabetes mellitus (haemoglobin A1C >6.2%)
    d. Chronic alcoholism (>6 ounces hard liquor daily for 10 or greater years)
3. Co-morbidities with anticipated survival <2 years or liver transplantation in <1 year
4. Liver transplantation
5. End-stage neuropathic disease (performance status >3, parenteral nutrition, bedsores)

6. New York Heart Association (NYHA) class IV (cardiac symptoms at rest & with minimal exertion)

7. Pregnancy or unwillingness to use contraception by women of child-bearing age

8. Renal insufficiency (creatinine clearance <30 mL/min)

9. Active or recent non-hemorrhoidal gastrointestinal bleeding (within past 18 months)

10. Current anti-coagulation therapy, non-study NSAID or aspirin use

11. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) or total bilirubin >3 times the upper limit of normal lab value

12. Non-steroidal or aspirin allergy/hypersensitivity

13. Thrombocytopenia (<100,000 platelets/mm^3)

14. Previous participation in this study

15. Inability or unwillingness of subject or legal guardian/representative to give written informed consent

The important exclusion criteria in the pivotal clinical trial are detailed below:

Co-morbidities with anticipated survival <2 years or liver transplantation in <1 yr.

Reason for exclusion: Patients with a disease severity different from inclusion criteria in clinical trials

Is it considered to be included as missing information: No

Rationale: estimated to not participate during the full duration of the clinical trial due to severity of clinical status

End-stage neuropathic disease (performance status >3, parenteral nutrition, bedsores)

Reason for exclusion: Patients with a disease severity different from inclusion criteria in clinical trials.

Is it considered to be included as missing information: No

Rationale: Patients estimated to not participate during the full duration of the clinical trial due to severity of clinical status.

NYHA class IV (cardiac symptoms at rest & with minimal exertion)

Reason for exclusion: Listed as a warning or contraindication in the product information for the study drug

Is it considered to be included as missing information: No

Rationale: Known safety risk.

Pregnancy or unwillingness to use contraception by women of child-bearing age

Reason for exclusion: Listed as a warning or contraindication in the product information for the study drug.

Is it considered to be included as missing information: No

Rationale: NSAID use during pregnancy is associated with intracranial haemorrhage and persistent pulmonary hypertension of the new-born due to premature closure of the ductus arteriosus.

Renal insufficiency (creatinine clearance <30 mL/min)

Reason for exclusion: Listed as a warning or contraindication in the product information for the study drug.

Is it considered to be included as missing information: No

Rationale: Since diflunisal is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored. In patients with severe renal impairment, the drug should not be used.

Active or recent non-hemorrhoidal gastrointestinal bleeding (within past 18 months)

Reason for exclusion: Listed as a warning or contraindication in the product information for the study drug.

Is it considered to be included as missing information: No

Rationale: Diflunisal should be used with caution in patients having a history of gastrointestinal haemorrhage, or ulcers. In patients with active peptic ulcers, the treatment should only be initiated only if the potential benefit of treatment outweighs the potential risk of adverse reactions. Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events, and close monitoring and standard prophylactic care, such as proton-inhibitors, to reduce risk of gastrointestinal effects caused by NSAIDs should be considered for patients at risk of gastrointestinal side-effects.

Current anti-coagulation therapy, non-study NSAID or aspirin use

Reason for exclusion: Listed as a warning or contraindication in the product information for the study drug.

Is it considered to be included as missing information: No

Rationale: NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. The dosage of oral anticoagulants may require adjustment.

AST, ALT or total bilirubin > three times the upper limit of normal lab value

Reason for exclusion: Listed as a warning or contraindication in the product information for the study drug.

Is it considered to be included as missing information: No

Rationale: May aggravate liver disease.

Thrombocytopenia (<100,000 platelets/mm^3)

Reason for exclusion: Listed as a warning or contraindication in the product information for the study drug.

Is it considered to be included as missing information: No

Rationale: NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

A total number of 64 individuals received diflunisal for a maximum duration of 2 years during the clinical trial referenced.

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

However, for the use of diflunisal in other indications, both clinical data and post-approval data are available and are referenced in the SmPC.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development programme
Breastfeeding women	
Patients with relevant co-morbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	As a result of their disease, patients with ATTR-FAP often have reduced renal and cardiac function, and such patients were included in the clinical trial. Only those with creatinine clearance <30 mL/min or heart failure of NYHA class IV were excluded. 21 patients randomised to diflunisal were assessed as having "abnormal" cardiac status at screening/enrolment. The total exposure to study drug for these patients was 10 016 patient-days.

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td></td><td>The available data does not allow for an accurate count of patients with impaired renal function.

Otherwise, the listed patient populations were not included in the clinical development programme for the indication ATTR-FAP.</td></tr>
<tr><td>Population with relevant different ethnic origin</td><td>Different ethnic origins identified in study population is Asian, black, white, multiracial.

For exposure, see Table SIII.3</td></tr>
<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>Subpopulations carrying relevant genetic polymorphisms have been included, identified and studied in this trial, please see table below:
<table>
<tr><th>ATTR variants</th><th>No of diflunisal-treated patients</th><th>Exposure (patient-days)</th></tr>
<tr><td>V30M</td><td>36</td><td>20 588</td></tr>
<tr><td>L58H</td><td>10</td><td>6 070</td></tr>
<tr><td>T60A</td><td>6</td><td>3 738</td></tr>
<tr><td>S50R</td><td>2</td><td>1 141</td></tr>
<tr><td>F64L</td><td>2</td><td>1 281</td></tr>
<tr><td>D38A</td><td>1</td><td>5</td></tr>
<tr><td>S77Y</td><td>1</td><td>245</td></tr>
<tr><td>V30G</td><td>1</td><td>727</td></tr>
<tr><td>F44S</td><td>1</td><td>223</td></tr>
<tr><td>E54Q</td><td>1</td><td>179</td></tr>
<tr><td>I84N</td><td>1</td><td>601</td></tr>
<tr><td>A97S</td><td>1</td><td>443</td></tr>
<tr><td>I107F</td><td>1</td><td>748</td></tr>
</table></td></tr>
<tr><td>Other</td><td>Not applicable</td></tr>
</table>

Part II: Module SV - Post-authorisation experience

Diflunisal was previously authorised in Sweden (between 1979 and 2007) and several other European countries as Donobid (tablet 250 mg) and subsequent generic versions. The post-authorisation experience of diflunisal products refers to safety data for other indications than ATTR-FAP and higher doses than those applicable for Attrogy. It should be noted that Donobid was withdrawn from the marketplace for commercial reasons, not because of any concerns regarding safety.

Although it has never been authorised for this indication, diflunisal is in current clinical practice widely used for the treatment of ATTR-FAP and is recommended in this role by a number of European guidelines (Adams D2016; Ando 2022; Conduluci 2021; Swedish Council for New TherapiesSwedish Council for New Therapies

SV.1 Post-authorisation exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Based on the characteristics and the mechanistic properties of the medicinal product, the potential of abuse or misuse for illegal purposes of the product in development is not considered applicable.

Part II: Module SVII - Identified and potential risks

The Applicant has not identified any new safety concern specific to the product relating to the new formulation or the new excipients. The route of administration is identical to the previously commercially available formulation that the Applicant has based the proposed risk management plan on and since no new clinical data have been generated, no new safety concerns have been raised.

Diflunisal is a difluorophenyl derivate of salicylic acid and is a non-selective NSAID. Diflunisal competitively inhibits both cyclooxygenase (COX) -1 and -2, with higher affinity for COX-1. The safety profile for NSAIDs is well known, and consistent with the warnings and contraindications proposed for Attrogy. These are aligned with the warnings and contraindications listed for Donobid when the product was authorised in Sweden and updated to reflect the current knowledge on NSAIDs.

Proposed contraindications include hypersensitivity to the active substance and, due to risk of cross-reaction, previous acute asthmatic attacks, urticaria, rhinitis or angioedema precipitated by acetylsalicylic acid or other NSAIDs, active gastrointestinal bleeding, severe heart failure and severe renal failure, severe hepatic impairment and use during third trimester of pregnancy.

Proposed warnings and precautions include gastrointestinal effects, renal effects, cardiovascular and cerebrovascular effects, masking signs of infections, platelet function, ocular effects, NSAIDs exacerbated respiratory disease, and hepatic effects.

SVII.1 Identification of safety concerns in the initial RMP submission

The active substance diflunisal has been used in Sweden and other EU and non-EU countries since 1979, primarily as an analgesic substance, but also off-label as a treatment for ATTR amyloidosis. With this initial RMP submission we do not expect the product to have any additional risks than those already identified with the substance and those identified in general safety profile of NSAIDs. These risks are well known and adequately managed and are not considered to constitute safety concerns.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks identified for NSAID products are already well known to health professionals and do not require additional pharmacovigilance activities or additional risk minimisation measures. For diflunisal, these risks include:

- Gastrointestinal effects; haemorrhage, ulceration and perforation
- Renal effects;
- Cardiovascular and cerebrovascular effects
- Masking of symptoms of infection
- Inhibition of platelet aggregation; prolonged bleeding time
- Ocular effects
- NSAIDs exacerbated respiratory disease
- Hepatic effects
- Foetal toxicity
- Hypersensitivity reactions

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

The above are known general NSAID risks that require no further characterisation and are followed up via routine pharmacovigilance (signal detection and adverse reaction reporting). The risk minimisation messages in the product information (Contraindications, Warnings and Precautions, Interactions) are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product would be authorised): see enclosed draft SmPC.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

None.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

The warnings and contraindications proposed for Attrogy are aligned with the warnings and contraindications listed for Donobid when the product was authorised in Sweden and updated to reflect current knowledge on NSAIDs. None of these risks are considered important, as discussed in SVII.1.1. No important missing information has been identified for diflunisal.

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable.

SVII.3.2. Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

The routine pharmacovigilance activities of adverse event reporting and signal detection are proposed as sufficient for this product.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are proposed by the Applicant for this product.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are planned by the Applicant.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk minimisation plan

The safety information in the proposed product information is aligned with the first approved diflunisal product, Donobid, and updated to reflect the current knowledge on NSAIDs. Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the Applicant.

V.1. Routine risk minimisation measures

The identified and potential risks for this product are well known and not considered to constitute safety concerns. Routine risk minimisation measures apply and are considered sufficient for management of these risks.

V.2. Additional risk minimisation measures

No additional risk minimisation measures apply.

V.3. Summary of risk minimisation measures

The identified and potential risks for Attrogy are well known and not considered to constitute safety concerns. Routine pharmacovigilance and routine risk minimisation measures apply and are considered sufficient for management of these risks.

Part VI: Summary of the risk management plan

Summary of risk management plan for Attrogy 250 mg film-coated tablets (diflunisal)

This is a summary of the risk management plan (RMP) for Attrogy 250 mg film-coated tablets. The RMP details important risks of Attrogy, how these risks can be minimised, and how more information will be obtained about Attrogy ‘s risks and uncertainties (missing information).

Attrogy's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Attrogy should be used.

This summary of the RMP for Attrogy 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 Attrogy's RMP.

I. The medicine and what it is used for

Attrogy is authorised for the treatment of Attrogy is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy. It contains diflunisal as the active substance and it is given by oral route of administration.

Further information about the evaluation of Attrogy’s benefits can be found in Attrogy’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage <link to the EPAR summary landing page>.

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

Important risks of Attrogy, together with measures to minimise such risks and the proposed studies for learning more about Attrogy'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 addition to these measures, information about adverse events is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR), 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 Attrogy is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

No important risks or missing information have been identified for Attrogy.

Important risks of Attrogy are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Attrogy. 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).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to a previously approved medicine containing diflunisal and updated to reflect current knowledge on NSAIDs.

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Attrogy.

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

There are no studies planned for Attrogy.

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance interface

Not applicable.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 - Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 5 - Protocols for proposed and ongoing studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

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Annex 8 – Summary of changes to the risk management plan over time

Not applicable.