**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Attrogy 250 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg diflunisal.

Excipient(s) with known effect

Each tablet contains 60 micrograms sunset yellow (E110).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light orange, capsule shape, biconvex coated tablet, engraved “D250” on one side and plain on the other side. The tablet is 6.35 mm in width and 14.29 mm in length.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

Posology

The recommended dose of diflunisal is one 250 mg tablet taken twice daily. The tablets should preferably be taken with food to reduce risk of gastro-intestinal adverse reactions (see section 4.4).

Special populations

*Elderly*
Diflunisal should be used with caution in elderly patients who are more prone to adverse reactions. No dose adjustment is required for elderly patients (≥65 years) in the absence of severe renal or hepatic insufficiency (see below and sections 4.3 and 4.4). Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

*Renal impairment*
Since diflunisal and its major metabolites are eliminated primarily by the kidneys, its half-life is extended in patients with reduced renal function. Diflunisal is contra-indicated in patients with renal impairment (GFR ≤30 ml/min) (see sections 4.3 and 4.4). No dose adjustment is required in patients with mild or moderate renal impairment.

*Hepatic impairment*
No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh A or B). Diflunisal is contra-indicated in patients with severe hepatic impairment (Child-Pugh C; see section 4.3).

*Paediatric population*
There is no relevant use of diflunisal in the paediatric population in the hATTR amyloidosis indication.

Method of administration

It is recommended that the tablets are swallowed whole, not crushed or chewed, due to the bitter taste. Patients who are taking antacids should leave a 2-hour interval between taking diflunisal and taking antacid medicines.

## 4.3 Contraindications

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

Previous acute asthmatic attacks, urticaria, rhinitis or angioedema precipitated by acetylsalicylic acid or other NSAIDs, due to risk of cross-reaction.

Active gastro-intestinal bleeding.

Severe heart failure (see section 4.4).

Severe renal impairment (GFR ≤30 ml/min) (see section 4.4).

Severe hepatic impairment (Child-Pugh C; see section 4.4).

Use during the third trimester of pregnancy and in breast-feeding mothers (see section 4.6).

## 4.4 Special warnings and precautions for use

Patients treated with NSAIDs long-term, such as diflunisal, should undergo regular medical supervision to monitor for adverse reactions. Older patients are particularly susceptible to the adverse reactions of NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal. Prolonged use of NSAIDs in these patients is not recommended. Where prolonged therapy is required, patients should be monitored regularly.

Use with concomitant NSAIDs including cyclo-oxygenase-2 specific inhibitors should be avoided (see section 4.5).

Gastro-intestinal effects

Diflunisal should be used with caution in patients having a history of gastro-intestinal haemorrhage, or ulcers. In patients with active peptic ulcers, the treatment should only be initiated if the potential benefit of treatment outweighs the potential risk of adverse reactions.

Gastro-intestinal 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 gastro-intestinal events. Close monitoring and standard prophylactic care, such as proton-pump inhibitors, to reduce risk of gastro-intestinal effects caused by NSAIDs should be considered for patients at risk of gastro-intestinal side-effects.

If gastro-intestinal bleeding or ulceration occurs, the treatment should be withdrawn.

Renal effects

There have been reports of acute interstitial nephritis with haematuria, proteinuria, and occasionally nephrotic syndrome in patients receiving diflunisal.

In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, administration of an NSAID may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with renal or hepatic dysfunction, diabetes mellitus, advanced age, extracellular volume depletion, congestive heart failure, sepsis, or concomitant use of any nephrotoxic medicinal product. An NSAID should be given with caution and renal function should be monitored in any patient who may have mildly or moderately reduced renal reserve. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Diflunisal has not been studied in ATTR amyloidosis patients with severe renal impairment or end-stage renal disease and must not be used in these patients (see section 4.3).

Since diflunisal and its major conjugated metabolites are eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored.

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for diflunisal.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diflunisal after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking, prolonged QTc interval).

Infections

Diflunisal should be used with extra care in the presence of existing infection, since it may mask the usual signs and symptoms of infection.

Platelet function

Diflunisal is an inhibitor of platelet function. Patients taking diflunisal who may be adversely affected by changes in platelet function, such as those with coagulation disorders or those taking anticoagulant medicines, should be carefully monitored.

Ocular effects

Because of reports of adverse eye findings with NSAIDs as listed in Section 4.8, it is recommended that patients who develop eye complaints during treatment with diflunisal have ophthalmological evaluations.

NSAIDs exacerbated respiratory disease

Diflunisal should be used with caution in patients suffering from, or with a previous history of bronchial asthma. NSAIDs have been reported to precipitate bronchospasm in some patients.

Hepatic effects

A patient on diflunisal with signs or symptoms suggesting liver disease, or in whom abnormal liver-function tests have occurred, should be evaluated for evidence of more severe effects on hepatic function. If abnormal liver tests persist or worsen, if signs or symptoms of liver disease develop, or if systemic manifestations such as eosinophilia or rash occur, diflunisal should be discontinued.

Excipients

Attrogy contains the azo colouring agent sunset yellow aluminium lake (E110) which may cause allergic reactions.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

## 4.5 Interaction with other medicinal products and other forms of interaction

The following combinations with diflunisal should be avoided:

*Acetazolamide*
Case reports suggest increased risk of metabolic acidosis when acetazolamide is used concomitantly with salicylic acid derivatives. Experimental studies show that salicylic acid derivatives, such as diflunisal, increase the free pharmacologically active concentration of acetazolamide.

*Anticoagulants*
NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Those receiving diflunisal who have pre-existing coagulation disorders or who are on concomitant anticoagulant therapy, should be carefully monitored. This applies to all anticoagulant therapies, including vitamin K antagonists (e.g. warfarin), heparins, and direct oral anticoagulants (DOACs, e.g. rivaroxaban). Adjustment of dosage of oral anticoagulants may be required.

*Indomethacin*
Diflunisal reduces renal clearance and glucuronidation of indomethacin which results in a substantial increase of the plasma levels of indomethacin.

*Methotrexate*
Diflunisal can produce renal dysfunction resulting in reduced excretion of methotrexate. Diflunisal may also compete for drug transporters responsible for excreting methotrexate (e.g. OAT1 and OAT3).

*Other NSAIDs and acetylsalicylic acid*
The concomitant use of diflunisal and other NSAIDs (including cyclooxygenase-2 selective inhibitors) is not recommended owing to the increased possibility of gastro-intestinal toxicity.

*Corticosteroids*
The risk of gastro-intestinal bleeding and ulceration associated with NSAIDs is increased when used with corticosteroids.

*Tacrolimus*
There is a possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

*Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs).*
There is an increased risk of gastro-intestinal bleeding when used concomitantly with NSAIDs.

Combinations that require special precaution or dose adjustments:

*Antacids*
Co-administration of aluminium hydroxide decreases the absorption of diflunisal. The medicinal products should be taken with a 2-hour interval.

*Ciclosporin*
Administration of NSAIDs concomitantly with ciclosporin has been associated with an increase in ciclosporin-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking ciclosporin, and renal function should be monitored carefully.

*Antihypertensives*
The antihypertensive effects of some antihypertensive medicinal products, including ACE inhibitors, beta-blocking agents and diuretics, may be reduced when used concomitantly with NSAIDs. Caution should, therefore, be exercised when considering the addition of NSAID therapy to the regimen of a patient taking antihypertensive therapy.

*Cardiac glycosides*
An increase in serum-digoxin concentration has been reported with concomitant use of acetylsalicylic acid, indomethacin and other NSAIDs. Therefore, when concomitant digoxin and NSAID therapy is initiated or discontinued, serum digoxin levels should be closely monitored.

*Diuretics*
NSAIDs may reduce the effect of diuretics. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

*Lithium*
Concomitant use of indomethacin with lithium produced a clinically relevant elevation of plasma lithium and reduction in renal lithium clearance in psychiatric patients and normal subjects with steady-state plasma lithium concentrations. This effect has been attributed to inhibition of prostaglandin synthesis and the potential exists for a similar effect with other NSAIDs. As a consequence, when an NSAID and lithium are given concomitantly, the patient should be observed carefully for signs of lithium toxicity. In addition the frequency of monitoring serum lithium concentrations should be increased at the outset of such combination therapy.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

From the 20$^{th}$ week of pregnancy onwards, diflunisal use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, diflunisal should not be given unless clearly necessary. If treatment with diflunisal is necessary, antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be performed from gestational week 20 until the third trimester of pregnancy (week 28) when diflunisal is contraindicated. Diflunisal must be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, diflunisal is contraindicated during the third trimester of pregnancy (see section 4.3).

Breast-feeding

Diflunisal is excreted in human milk to such an extent that effects on the breastfed newborn / infant are likely. Diflunisal is contraindicated during breast-feeding (see section 4.3).

Fertility

The use of diflunisal may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation in infertility, withdrawal of diflunisal should be considered.

## 4.7 Effects on ability to drive and use machines

Diflunisal is expected to have no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most common and most important adverse reactions reported for diflunisal are gastro-intestinal.

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA System Organ Class (SOC) and frequency categories using the standard convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥1/1,000 to < 1/100), Rare (≥1/10,000 to < 1/1,000), Very rare (<1/10,000) and Not known (frequency cannot be estimated from the available data).

*Table 1 Tabulated list of adverse reactions*

| System Organ Class | Very common | Common | Uncommon | Very rare |
|---|---|---|---|---|
| Infections and infestations | | Viral gastroenteritis | | |
| Blood and lymphatic system disorders | | | Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia | |

| System Organ Class | Very common | Common | Uncommon | Very rare |
|---|---|---|---|---|
| Immune system disorders | | | Acute anaphylactic reaction with bronchospasm, angioedema, hypersensitivity vasculitis, hypersensitivity syndrome | |
| Psychiatric disorders | | | Depression, hallucinations, nervousness, confusion | |
| Nervous system disorders | | Headache, dizziness, somnolence, insomnia | Vertigo, light headedness, paraesthesiae | |
| Eye disorders | | Ocular hypertension | Transient visual disturbances including blurred vision | |
| Ear and labyrinth disorders | | Tinnitus | | |
| Cardiac disorders | | Cardiac failure | Palpitations, syncope | |
| Vascular disorders | | Hypertension | | Allergic vasculitis |
| Respiratory, thoracic and mediastinal disorders | | | Dyspnoea | Rhinitis, asthma |
| Gastrointestinal disorders | Dyspepsia | Gastrointestinal pain, diarrhoea, nausea, vomiting, constipation, flatulence, gastrointestinal perforation and bleeding, gastroesophageal reflux disease | Peptic ulcer, anorexia, gastritis, haematemesis, melaena, ulcerative stomatitis, exacerbation of colitis and Crohn's disease | |
| Hepatobiliary disorders | | | Jaundice sometimes with fever, cholestasis, liver-function abnormality, hepatitis | Raised transaminases |
| Skin and subcutaneous tissue disorders | | Rash, sweating, dermatitis, erythema | Pruritus, dry mucous membranes, stomatitis, photosensitivity, urticaria, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis | |
| Musculoskeletal and connective tissue disorders | | | Muscle cramps | |
| Renal and urinary disorders | | Renal failure, proteinuria | Dysuria, renal impairment, interstitial nephritis, haematuria, nephritic syndrome | |

| System Organ Class | Very common | Common | Uncommon | Very rare |
|---|---|---|---|---|
| General disorders and administration site conditions | | Fatigue, oedema, peripheral oedema, chest pain, early satiety, | Asthenia, loss of apetite | |
| Investigations | | Occult blood positive, haematocrit decreased | | |

An apparent hypersensitivity syndrome has been reported in a few patients treated with diflunisal. This syndrome manifests the following symptoms: fever, chills, cutaneous reactions of different severity, changes in liver function, jaundice, leucopenia, thrombocytopenia, eosinophilia, disseminated intravascular coagulation, renal impairment, adenitis, arthralgia, myalgia, arthritis, anorexia, disorientation.

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 Appendix V.

### 4.9 Overdose

The most common signs and symptoms observed with overdosage are drowsiness, dizziness, vomiting, nausea, epigastric pain, gastro-intestinal bleeding, diarrhoea, hyperventilation, tachycardia, sweating, tinnitus, disorientation, stupor, excitation and coma. Diminished urine output and cardiorespiratory arrest have also been reported. The lowest dose of diflunisal alone at which death was reported was 15 g. Death has also been reported from a mixed drug overdose that included 7.5 g diflunisal.

In the event of recent overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be observed carefully and given symptomatic and supportive treatment. To facilitate urinary elimination of the drug, attempt to maintain renal function. Because of the high degree of protein binding, haemodialysis is not recommended. Monitor renal and liver function as well as the patient's clinical condition. Convulsions should be treated with antiseizure medication.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Salicylic acid and derivatives.
ATC code: NO2BA11

Mechanism of action

Diflunisal is a potent stabiliser of tetrameric transthyretin (TTR), which effectively stabilises the tetramer against dissociation to the TTR monomers which are responsible for amyloidosis pathology.

Clinical efficacy and safety

*Methodology*

The efficacy and safety of diflunisal was investigated in an international, randomised, double-blind, placebo-controlled clinical trial. N=130 patients were randomised in a 1:1 manner to receive 250 mg

diflunisal twice daily (N=64) or matching placebo (N=66) for 2 years. Patients were between 18 and 75 years old, had biopsy-proven amyloid deposition, mutant TTR genopositivity, clinical signs of peripheral or autonomic neuropathy and routinely spent more than 50% of waking hours out of bed or chair (ECOG performance status <3). Exclusions included alternative causes of sensorimotor polyneuropathy, limited survival expectation (<2 years), prior liver transplantation, severe congestive heart failure (class IV NYHA), renal insufficiency (estimated creatinine clearance <30 mL/min) and ongoing anticoagulation. The mutation distribution of the patients studied was V30M (n=71), L58H (n=15), T60A (n=15), S50R (n=4), F64L (n=4), D38A, S77Y, E89Q & V122I (n=2 each), V30G, V32A, K35N, K35T, E42G, F44S, T49P, E54Q, V71A, Y78F, I84N, A97S & I107F (n=1 each).

The primary endpoint, the difference in polyneuropathy progression between treatments, was measured by the Neuropathy Impairment Score plus 7 nerve tests (NIS+7). NIS+7 scores range from 0 (no neurologic deficits) to 270 points (no detectable peripheral nerve function).

*Results*

Patients had a mean age of 60.2 years and a mean NIS+7 score of 55.3 units at baseline. 66.9% of patients were male and 78.5% were white. 122/130 patients (93.8%) had FAP Stage 1 or 2 disease. Baseline characteristics, TTR genotyping, and polyneuropathy staging were similar between treatment groups. Nearly one third (30.8%) of the patients required support when walking and 4 patients in each treatment group were wheelchair-bound (FAP Stage 3). Outcome measures were not statistically different between groups at enrolment.

51.5% of patients discontinued study drug before completing the 2-year period of treatment (42.2% of patients randomised to diflunisal and 60.6% of patients randomised to placebo). Disease progression and orthotopic liver transplantation were the leading reasons for drop out. Analysis indicated that drop out was preceded by significantly worse disease state. Those patients who dropped out after 12 months had significantly higher 12-month NIS+7 score. The ITT analysis is presented below:

*Table 2* ***Results of longitudinal analysis in the ITT population***

| **Variable** | **Baseline score** | | **Mean placebo-subtracted difference at Month 12 (95% CI)** | **Mean placebo-subtracted difference at Month 24 (95% CI)** |
|---|---|---|---|---|
| | **Diflunisal** | **Placebo** | | |
| NIS+7 (primary endpoint) | 51.57 | 59.00 | 6.4<br>(1.2, 11.6)<br>p=0.017 | 18.0<br>(9.9, 26.2)<br>p<0.001 |

Results were irrespective of gender, geographical region, and disease severity at entry.

The majority of the patients studied (77.7%) had one of the 3 most common single site TTR variants. There are at least 100 other potential single site mutations associated with the potential to cause TTR amyloidosis. Of these, 19 were represented in the trial. The mechanism of action of diflunisal is expected to be translatable to all TTR variants and the results of the trial are expected to be valid regardless of the underlying mutation.

## 5.2 Pharmacokinetic properties

Absorption

Diflunisal is close to completely absorbed when used in therapeutic doses. Peak plasma concentrations occur within 2 to 3 hours. Food affects the rate of diflunisal absorption but not the extent of absorption.

Distribution

The degree of protein binding in plasma is high; approximately 98-99% of diflunisal in plasma is bound to proteins.

At the clinical dose of 250 mg twice daily, steady state concentrations of diflunisal in plasma are reached after 4-5 days and the plasma elimination half-life of diflunisal is 8-10 hours. At higher repeated twice daily doses of diflunisal, time to steady state concentrations of diflunisal and plasma elimination half-life are increased dose-proportionately.

Metabolism

No metabolites of diflunisal have been identified in human plasma. Diflunisal is extensively metabolised mainly in the liver by phase 2 conjugation enzymes and its conjugates have been identified in urine.

Elimination

In humans, diflunisal is mainly metabolised to form two glucuronide conjugates and one sulphate conjugate, which are water soluble and excreted in the urine. Diflunisal is also excreted in smaller amounts in the urine, approximately 5% of dose administered. Age, weight, gender and ethnicity are not expected to have a significant effect on elimination of diflunisal.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential, which is additional to those already mentioned in other sections of this Summary of Product Characteristics. However, based on doses/human equivalent doses, exposures at the No Observed Adverse Effect Levels (NOAEL) in the different studies were only slightly higher or even below those in patients receiving the maximum recommended human dose.

Reproduction and development toxicity

Diflunisal has shown no evidence of effects on fertility in rats but has been shown to increase the length of the gestation period in rats. Diflunisal has shown no evidence of developmental toxicity in mice, rats and cynomolgus monkeys. Severe maternal haemolytic anaemia was uniquely induced in rabbits, resulting in developmental toxicities in foetuses.

Juvenile toxicity

Data suggest that diflunisal is more toxic to neonatal rats and dogs than to adult animals.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose (E460) (PH 101)
Pre-gelatinised starch (E1422)
Croscarmellose sodium (E468)

Silica, hydrophobic colloidal (E551)
Magnesium stearate
Hydroxypropyl methylcellulose (E464) 2910 E5/Hypromellose
Macrogol 3350 (E1521)
Titanium dioxide (E171)
Sunset Yellow Aluminium Lake (E110)
Purified water

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

### 6.5 Nature and contents of container

HDPE bottle with polypropylene child-resistant tamper-evident screw cap with a liner. Pack size of 100 film-coated tablets.

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Purpose Pharma International AB
Grev Turegatan 13b
114 46 Stockholm
Sweden

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1929/001

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

## 10. DATE OF REVISION OF THE TEXT

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

# ANNEX II

**A. MANUFACTURER(S) 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(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

SkyePharma Production S.A.S
Zone Industrielle Chesnes Ouest
55 Rue Du Montmurier
38070 Saint-Quentin-Fallavier
France

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## 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.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (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.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**CARTON AND BOTTLE LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT

Attrogy 250 mg film-coated tablets
diflunisal

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 250 mg of diflunisal

## 3. LIST OF EXCIPIENTS

Sunset yellow FCF (E 110)

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

100 tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.
See leaflet for further information.

## 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 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

Purpose Pharma International AB
114 46 Stockholm
Sweden

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1929/0001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Attrogy [outer packaging only]

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the patient**

**Attrogy 250 mg film-coated tablets**
diflunisal

**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.
- 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. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Attrogy is and what it is used for

Attrogy contains the active substance diflunisal.

Attrogy is used in:
- adults for the treatment of stage 1 familial transthyretin amyloidosis with polyneuropathy, an inherited disease in which fibres called amyloid fibrils build-up in tissues around the body including around the nerves. In stage 1, people experience symptoms such as tingling, numbness or weakness, especially in the legs or feet;

- adults for the treatment of stage 2 familial transthyretin amyloidosis with polyneuropathy, an inherited disease in which fibres called amyloid fibrils build-up in tissues around the body including around the nerves. In stage 2, people may experience more severe tingling, numbness or weakness in the hands and feet, making it harder to walk or perform everyday tasks.

In patients with familial transthyretin amyloidosis, a protein called transthyretin is defective and breaks down easily. The broken down protein forms a fibrous substance, known as amyloid fibrils, that build up in tissues and organs around the body, preventing them from working normally.

Attrogy stabilises transthyretin by attaching to it so that it becomes stable and no longer breaks apart. This prevents pieces of the abnormal protein from forming the harmful amyloid fibrils.

## 2. What you need to know before you use Attrogy

**Do not use Attrogy**
- if you are allergic to diflunisal or any of the other ingredients of this medicine (listed in section 6).
- if you have previously experienced symptoms like acute asthma, rash, runny nose or swelling of the skin after taking medicines containing acetylsalicylic acid (a substance present in many medicines used to relieve pain and lower fever) or non-steroidal anti-inflammatory drugs

(NSAIDs) (e.g. ibuprofen, naproxen, diclofenac, celecoxib) used for fever, pain and inflammation.
- if you have bleeding in your stomach or intestines
- if you have heart failure
- if you have severe kidney problems
- if you have severe liver problems
- if you are in the 3rd trimester of pregnancy
- if you are breast-feeding

**Warnings and precautions**
Talk to your doctor before using Attrogy
- If you are taking NSAID medicines (e.g. ibuprofen, naproxen, diclofenac or celecoxib), especially if you are over 65 years of age, you should discuss with your doctor before taking this medicine
- if you have, or have had, ulcers in your stomach or intestines
- if you have a history of heart or blood circulation problems such as high blood pressure, if your heart does not pump blood as well as it should causing shortness of breath, tiredness and ankle swelling, heart disease caused by narrowing or blockage of blood vessels supplying the heart muscle, reduced blood flow in arteries of the legs and arms, disease of the blood vessels supplying the brain
- if you have raised levels of lipids (e.g. cholesterol) in your blood, if you are a smoker and/or if you have a type of electrical abnormality of the heart called “long QT syndrome”
- if your kidneys have reduced function or if you have diabetes, as there is a risk of developing problems with your kidneys if you become dehydrated. For the same reason, ask a doctor before use if you have not been drinking fluids or have lost fluid due to continuous vomiting or diarrhoea.
- if your heart or liver have reduced function or have abnormal liver function testsif you have problems with how your blood clots or if you are taking medicines used to thin the blood
- if you have signs or symptoms of an infection
- if you have problems with your eyes or if you get any new eye problems as it is recommended that you have your eyes checked
- if you have or have previously had asthma or breathing problems

**Children and adolescents**
Attrogy is not intended for use in children or adolescents less than 18 years of age as they do not have symptoms of familial transthyretin amyloidosis

**Other medicines and Attrogy**
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. It is especially important if you use any of the following medicines:
- antacids containing aluminium hydroxide (used for heartburn). If you are taking antacids, you should leave a 2-hour interval between taking Attrogy and taking antacid medicines,
- acetazolamide (used for glaucoma),
- methotrexate (used for cancer and rheumatism),
- warfarin and other oral anticoagulant and anti-platelet medicines (used to prevent blood clots),
- acetylicsalicylic acid (a substance present in many medicines used to relieve pain and lower fever),
- indomethacin and other NSAIDs (used for relief of fever, pain and inflammation),
- ciclosporin and tacrolimus (used to prevent rejection of transplanted organs),
- medicines used for high blood pressure or arrhythmias,
- diuretics e.g. hydrochlorothiazide, furosemide, amiloride (used for fluid-retention),
- lithium (used for bipolar disorder),
- corticosteroids (used to treat inflammation),
- selective serotonin reuptake inhibitors commonly known as SSRIs (used for depression).

**Pregnancy, breast-feeding and fertility**

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

Pregnancy

You should not take Attrogy during the first 6 months of pregnancy unless absolutely necessary and advised by your doctor. **Do not** take Attrogy if you are in the last 3 months of pregnancy.

This medicine could harm your unborn child or cause problems at delivery. It can cause kidney and heart problems in your unborn baby. It may affect you and your baby's tendency to bleed and may delay or prolong labour.

If you take this medicine for more than a few days from week 20 of pregnancy onwards, your doctor will recommend additional monitoring. This is because Attrogy can cause kidney problems in your unborn baby that may lead to low levels of the fluid surrounding the baby in the womb (oligohydramnios) or can narrow a blood vessel (ductus arteriosus) in the heart of the baby. You must stop taking this medicine before week 28 of your pregnancy.

Breast-feeding

Do not use Attrogy if you are breast-feeding. The active substance in Attrogy, diflunisal, passes into human breast milk.

Fertility

The use of Attrogy may reduce fertility in women and is not recommended in women attempting to conceive.

**Driving and using machines**
This medicine is not expected to influence your ability to drive or use machines.

**Attrogy contains Sunset yellow FCF (E 110)**
May cause allergic reactions.

**Attrogy contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

## 3. How to use Attrogy

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

The recommended dose is one 250 mg tablet taken twice daily.

It is recommended that you swallow the tablets whole. It is not recommended to crush or chew the tablets due to a potential bitter taste. You should preferably take the tablets together with food to reduce the risk of unwanted effects on the stomach and intestines. If you are taking antacids, then allow 2 hours before taking Attrogy tablets.

**If you take more Attrogy than you should**
Contact a doctor or pharmacist immediately for advice.

**If you forget to take Attrogy**
If you have missed a dose, wait until it is time to take the next dose. Then take the tablet as normal. Do not take a double dose to make up for a forgotten tablet.

## 4. Possible side effects

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

**Serious side effects**
Stop taking Attrogy and contact your physician immediately if you experience any of the following side effects.

**Uncommon** (may affect up to 1 in 100 people)
- swelling of the face, lips, tongue,throat, arm or legs. These may be symptoms of angioedema (sudden swelling that is often caused by an allergic reaction)
- a wide-spread severe rash with peeling skin which may be accompanied by fever, flu like symptoms, blisters in the mouth, eyes, and/or genitals. These may be symptoms of a life-threatening reaction known as Stevens Johnson syndrome.

**Common** (may affect up to 1 in 10 people):
- signs of intestinal bleeding such as passing blood in your faeces (stools/motions), black tarry stools, vomiting blood or dark particles that look like coffee grounds.

**Other side effects**

**Very common** (may affect more than 1 in 10 people)
- Indigestion or heartburn (dyspepsia)

**Common** (may affect up to 1 in 10 people):
- viral infection of the stomach
- stomach and gut (gastrointestinal) pain
- diarrhoea
- feeling sick (nausea)
- vomiting
- constipation
- gas (flatulence)
- a tear (perforation) in the stomach or gut
- bleeding in the stomach or gut
- backward flow of stomach acid contents into the tube that connects the mouth to the stomach (gastro-oesophageal reflux disease)
- feeling full after eating a small amount of food (early satiety)
- headache
- dizziness
- high eye pressure (ocular hypertension)
- sleeping difficulties (insomnia)
- tiredness (fatigue)
- feeling sleepy (somnolence)
- rash
- sweating
- ringing in the ears (tinnitus)
- kidney (renal) failure
- heart (cardiac) failure
- chest pain
- inflammation of the skin (dermatitis)

- reddening of the skin (erythema)
- high blood pressure (hypertension)
- fluid retention (oedema).
- decrease in the percentage of red blood cells (haematocrit decreased)
- hidden blood in the stool (occult blood positive)
- abnormally high level of protein in urine (proteinuria)

**Uncommon** (may affect up to 1 in 100 people)

- sudden, severe allergic reaction with excessive contraction of the airway muscle causing difficulty breathing (acute anaphylactic reaction with bronchospasm)
- fluid retention around the heart (angioedema)
- fever, chills, muscle or joint pain, abnormal liver or kidney tests, abnormal blood tests, skin rashes or yellowing of the skin (hypersensitivity syndrome)
- an ulcer in the stomach or small intestine (peptic ulcer)
- loss of appetite
- inflammation of the stomach lining (gastritis)
- vomiting blood (haematemesis)
- inflammation of small blood vessels due to allergic reactions (hypersensitivity vasculitis)
- life-threatening reaction with flu-like effects and blistering in the skin, mouth eyes and genitals (toxic epidermal necrolysis)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or "bulls-eye" with a dark red centre surrounded by paler red rings (erythema multiforme)
- a severe skin condition that causes widespread peeling and shedding of the top layers of the skin with fever (exfoliative dermatitis) inflammation of the mouth and lips (ulcerative stomatitis)
- inflammation of the lining of the mouth (stomatitis)
- sensitivity to light (photosensitivity)
- itching (pruritus)
- dryness of the moist body surfaces, such as the lining of the mouth (mucous membranes)
- inflammation around the kidney tubules (interstitial nephritis)
- yellowing of the skin and eyes (jaundice) sometimes in combination with fever
- reduced flow of bile from the liver due to a blockage (cholestasis)
- abnormal liver function
- inflammation of the liver (hepatitis)
- worsening of inflammation of the colon (exacerbation of colitis)
- worsening of Crohn's disease
- tingling or a pricking sensation of the skin, nettle rash (urticaria),
- painful urination (dysuria)
- kidney problems (renal impairment)
- a combination of symptoms including swelling, high blood pressure and reduced urine output, due to inflammation of the filtering units in the kidneys (nephritic syndrome)
- blood in the urine (haematuria)
- black tarry stool (melaena)
- feeling weak (asthenia)
- palpitations
- fainting (syncope)
- a spinning sensation (vertigo)
- light headedness
- shortness of breath (dyspnoea)
- feeling nervous
- depression
- hallucinations
- confusion
- temporary visual disturbances including blurred vision

- muscle cramps
- pins and needles (paraesthesiae)
- low levels of blood platelets, components that help the blood to clot (thrombocytopenia)
- low levels of neutrophils, a type of white blood cell (neutropenia)
- very low levels of a type of white blood cell called granulocytes which are important for fighting infection (agranulocytosis)
- bone marrow stops producing new blood cells (aplastic anaemia)
- excessive breakdown of red blood cells (haemolytic anaemia)

**Very rare** (may affect up to 1 in 10,000 people)
- runny nose (rhinitis)
- asthma
- increased levels of liver enzymes (transaminases) as seen in blood tests
- inflammation of the small blood vessels due to an allergy (allergic vasculitis).

**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 Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store Attrogy

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 label and carton after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

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 Attrogy contains**
- The active substance is diflunisal. 1 tablet contains 250 mg of diflunisal.
- The other ingredients are microcrystalline cellulose (E460), pre-gelatinised starch (E1422), croscarmellose sodium (E468), silica, hydrophobic colloidal (E551), magnesium stearate, hydroxypropyl methylcellulose (E464), macrogol 3350 (E1521), titanium dioxide (E171), Sunset yellow FCF (E 110), purified water.
  This medicine contains Sunset yellow FCF (E 110), see section 2.

**What Attrogy looks like and contents of the pack**
This medicine is a light orange, biconvex film-coated tablet, in a plastic bottle with a plastic screw cap. It is available in packs containing 100 tablets.

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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.