10 June 2025
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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Attrogy (diflunisal)
Treatment of ATTR amyloidosis
EU/3/22/2640

Sponsor: Purpose Pharma International AB

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Product and administrative information

Product	
Designated active substance(s)	Diflunisal
Other name(s)	Diflunisal
International Non-Proprietary Name	Diflunisal
Tradename	Attrogy
Orphan condition	Treatment of ATTR amyloidosis
Sponsor's details:	Purpose Pharma International AB Grev Turegatan 13b Engelbrekt 114 46 Stockholm Sweden
Orphan medicinal product designation procedural history	
Sponsor/applicant	Turnkey Pharmaconsulting Ireland Limited
COMP opinion	12 May 2022
EC decision	24 June 2022
EC registration number	EU/3/22/2640
Post-designation procedural history	
Transfer of sponsorship	Transfer from Turnkey Pharmaconsulting Ireland Limited to AO Pharma AB – EC decision of 28 October 2022
Sponsor's name change	Name change from AO Pharma AB to Purpose Pharma International AB – EC letter of 24 January 2025
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Fátima Ventura / Ewa Balkowiec Iskra
Applicant	Purpose Pharma International AB
Application submission	15 January 2024
Procedure start	01 February 2024
Procedure number	EMA/H/C/006248/0000
Invented name	Attrogy
Therapeutic indication	Attrogy is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy. Further information can be found in the European public assessment report (EPAR) on the Agency's website: Attrogy | European Medicines Agency (EMA)
CHMP opinion	25 April 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Joao Rocha / Elisabeth Johanne Rook
Sponsor's report submission	27 January 2025
COMP discussion and adoption of list of questions	13-15 May 2025
Oral explanation	10 June 2025
Sponsor's removal request	10 June 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2022 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing diflunisal was considered justified based on published clinical data suggesting symptomatic improvements in patients with polyneuropathy and cardiomyopathy manifestations of the condition;
- the condition is life-threatening and chronically debilitating in particular due to the development of neuropathy and cardiomyopathy;
- the condition was estimated to be affecting approximately 1.4 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing diflunisal will be of significant benefit to those affected by the condition. The sponsor has provided published clinical data suggesting symptomatic improvements in patients with advanced polyneuropathy (stage 3) as well as cardiomyopathy manifestations of the condition which cannot be expected from currently authorized medicinal products. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing diflunisal as an orphan medicinal product for the orphan condition: treatment of ATTR amyloidosis.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Transthyretin-mediated (ATTR) amyloidosis is a rare, progressive disease caused by the misfolding of the transthyretin (TTR) protein. This protein is primarily produced in the liver and normally helps transport vitamin A and thyroxine (a thyroid hormone) in the blood.

In ATTR amyloidosis, the misfolded TTR proteins aggregate into amyloid fibrils, which deposit in various tissues and organs, leading to their dysfunction. There are two main types of ATTR amyloidosis:

- Hereditary (hATTR): This form is caused by mutations in the TTR gene and can affect multiple organs. hATTR can be classified into cardiac, neurologic, or mixed forms, depending on the observed disease phenotype. Several TTR gene variants have been associated with hATTR, with the Val30Met variant being the most common worldwide. The Val30Met variant primarily causes neuropathic symptoms when associated with early disease onset (before 50 years of age), while both neurologic and cardiac involvement is observed in late-onset V30M. hATTR is generally inherited in an autosomal dominant pattern. The target patient population for diflunisal are patients with hereditary forms of the condition (hATTR), presenting with polyneuropathy.
- Wild-type (wtATTR): This form occurs without any genetic mutations and primarily affects the heart. The average age at diagnosis for wtATTR is around 75 years and the great majority of cases reported are males. The condition has previously been known as Senile Systemic Amyloidosis.

The approved therapeutic indication "*Attrogy is indicated for the treatment of familial amyloid polyneuropathy (FAP) stage 1 or stage 2 transthyretin amyloidosis in adults with polyneuropathy"* falls within the scope of the designated orphan condition "Treatment of transthyretin-mediated amyloidosis"

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

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 (Adams et al, 2016).

The condition is considered life-threatening and chronically debilitating by the COMP, in particular due to the development of neuropathy and cardiomyopathy.

Number of people affected or at risk

The sponsor proposes a prevalence estimate of "*not more than 1 per 10,000 persons*", in line with their previous proposal during the initial orphan designation. This estimate is lower than value agreed by the COMP during the initial orphan designation for this product in June 2022, which was "*approximately 1.4 in 10,000 persons*".

The sponsor states that their literature search did not reveal any additional publications which included a prevalence estimate for an EU country, as compared to those identified in preparation of their application for initial orphan designation in 2022. Therefore, the conclusions reached by the sponsor, based on the same epidemiologic data.

In brief, four relevant publications were identified which reported data from 11 EU countries (Parman et al, 2016; Schmidt et al, 2018; Auer-Grumbach et al, 2020; Pozsonyi et al, 2021). The mean of the 11 country-specific prevalence values is:

- 1492 / 11 = 135.6 per million equivalent to approximately 1.4 per 10,000.

However, this apparent prevalence is artificially inflated by data from two countries with small populations (Portugal and Sweden). These countries account for 14,404 of the overall total of 16,938 estimated cases across all 11 countries covered (85%). According to the sponsor, a more representative estimate can be made by calculating the population-weighted average as follows:

- 16,938 / 321.8 = 52.6 per million equivalent to approximately 0.5 per 10,000.

The sponsor concludes that for potential under-reporting and for the absence of data from several EU countries comprising about 30% of the EU population, the formal estimate of prevalence for the purposes of orphan designation is not more than 1 per 10,000.

The COMP noted that the epidemiology of ATTR amyloidosis (comprising both hATTR and wtATTR) is currently changing rapidly. The recent increase in the use of non-invasive diagnostics for ATTR-amyloidosis and the introduction of treatment options not only increases the proportion of patients with better prognosis compared to the literature predating these developments, but also overall raises awareness of the condition in clinical practice. All these factors have a major impact on the prevalence. An up-to-date assessment of prevalence is therefore considered necessary by the COMP. The prevalence should be estimated for the whole condition, which includes patients with wild-type ATTR-amyloidosis cardiomyopathy. For the estimation and presentation of the prevalence estimate the sponsor is advised to refer to the "*Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation*". The sponsor should justify the inclusion and choice of sources selected for the prevalence estimation and describe the methodology used for these calculations. Due to significant uncertainties surrounding many of the underlying assumptions, the sponsor should elaborate on the prevalence estimate for the proposed orphan condition and is asked to comment on the accurate reflection of current developments (e.g. increasing use of scintigraphy and ageing population).

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The current pharmacological treatments approved in the EU for ATTR are the TTR tetramer stabilising agent tafamidis and the TTR silencing agents inotersen, patisiran, vutrisiran and eplontersen (Table 1):

Table 1. Authorised Medicines for the Treatment of ATTR Amyloidosis in the EU

Proprietary name	Generic name	Therapeutic indication	MAA approval date in EU
VYNDAQEL	Tafamidis	Treatment of transthyretin amyloidosis in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment (VYNDAQEL 20 mg soft capsules)	16 November 2011
		Treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) (VYNDAQEL 61 mg soft capsules)	
TEGSEDI	Inotersen	Treatment of Stage 1 or Stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)	06 July 2018
ONPATTRO	Patisiran	Treatment of hereditary transthyretin-mediated amyloidosis (hATTR)[a] in adult patients with Stage 1 or Stage 2 polyneuropathy	27 August 2018
AMVUTTRA	Vutrisiran	Treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with Stage 1 or Stage 2 polyneuropathy	15 September 2022
WAINZUA	Eplontersen	Wainzua is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (ATTRv) in adult patients with stage 1 or stage 2 polyneuropathy.	March 2025

Since the initial orphan designation, two new treatments for ATTR amyloidosis have been authorised in the EU, i.e. the silencers vutrisiran and eplontersen. The sponsor did not include eplontersen in their list of authorized products and did not discuss the significant benefit of their product vis a vis eplontersen.

For the purpose of this procedure, inotersen, patisiran, vutrisiran and eplontersen are considered satisfactory methods as they have fully overlapping indication-wordings with diflunisal (i.e. treatment of ATTR patients with stage 1 and 2 polyneuropathy).

Tafamidis on the other hand is only authorized for the treatment of patients with stage 1 polyneuropathy. Therefore, diflunisal is considered to provide a benefit in a patient population which is not covered by the indication of tafamidis, i.e. stage 2 polyneuropathy. This is reflected in the therapeutic indication wording for diflunisal, i.e. *"Attrogy is indicated for the treatment of familial amyloid polyneuropathy (FAP) stage 1 or stage 2 transthyretin amyloidosis in adults with polyneuropathy"*. In the pivotal clinical study with diflunisal, around 25% of patients had familial amyloidotic polyneuropathy (FAP) stage 2 and around 6% of patients had FAP stage 3, at time of enrolment. All other patients had FAP stage 1.

Significant benefit

Protocol assistance addressing the significant benefit aspect was not requested. The sponsor argues that this is primarily because the data supporting the diflunisal MAA were generated prior to the orphan designation application and before authorisation of any alternative drugs in the ATTR amyloidosis indication, i.e. the study data from the pivotal placebo-controlled trial published by Berk et al., in 2013.

As stated above, the significant benefit of diflunisal needs to be established over currently authorized therapies which have a fully overlapping indication wording, i.e. inotersen, patisiran, vutrisiran and eplontersen.

No arguments were provided by the sponsor to support the significant benefit over eplontersen, which was authorized in March 2025 in the EU.

The sponsor argues that in relation to inotersen, patisiran and vutrisiran, significant benefit is based on the grounds of (a) evidence of efficacy in a broader patient population, i.e. patients with FAP Stage 3 disease and (b) major contribution to patient care (MCPC).

Significant benefit vs inotersen, patisiran and vutrisiran based on efficacy in FAP stage 3 patients

The pivotal diflunisal study was not designed to establish efficacy in FAP Stage 3 (PND Stage 4) patients, although patients with advanced disease were not excluded from participation. 8 such patients were enrolled and 4 were assigned to each treatment group. All 4 of the patients assigned to placebo discontinued the trial, consequently there are no placebo data available for FAP Stage 3 patients at the 2-year primary endpoint assessment. Lacking a corresponding placebo group, the sponsor has descriptively compared the three observed patients with FAP stage 3 randomised to diflunisal to the placebo arm including all FAP stages. One patient randomised to diflunisal also discontinued early and contributed no post-baseline data.

The COMP considers that the data is too limited and the comparison methodology not suitable to generate sufficient evidence for demonstrating an effect of diflunisal in FAP 3 patients. Patients randomised to placebo of all stages are not considered to be a suitable control group for patients randomised to diflunisal in FAP 3. Furthermore, the COMP took note of the CHMP conclusion to not grant the inclusion of patients with FAP stage 3 in the 4.1. therapeutic indication of the diflunisal SmPC. This decision was based on both efficacy and safety considerations. Correspondingly, the presented evidence is not considered to support the significant benefit claim of diflunisal vis a vis inotersen, patisiran and vutrisiran in a broader patient population, i.e. patients with FAP Stage 3 disease.

Significant benefit vs inotersen based on major contribution to patient care

The sponsor states that there are no clinical trials directly comparing diflunisal and inotersen, and comparison of data across trials is not feasible due to significant trial design and population differences.

The applicant’s claim of significant benefit is made on the grounds that diflunisal offers a major contribution to patient care in comparison to inotersen. Inotersen is given via once weekly subcutaneous injection. Its use is associated with a risk of thrombocytopenia that requires regular and frequent monitoring. These monitoring recommendations associated with inotersen therapy place a significant further burden on patients and family members, in terms of discomfort from additional, and possibly frequent, blood draws and the associated travel requirement.

In the pivotal diflunisal trial one patient in the treatment group (1.6%) and one patient in the placebo group (1.5%) experienced thrombocytopenia. The events were described as moderate (in the diflunisal patient) and mild (in the placebo patient). In both cases it was considered non-serious and unlikely to be related to study drug.

The COMP does not consider that the arguments provided by the sponsor are sufficient to support the significant of diflunisal over inotersen based on MCPC due to the following:

- To be regarded as making a major contribution to patient care, the product should at least be equivalent in terms of efficacy, safety and benefit/risk balance as compared with the authorised medicinal products, reference is made to the Commission notice on the application of Articles 3, 5 and 7 of the EU Orphan Regulation (2016/C 424/03). No data has been provided by the sponsor to support this requirement. In the absence of direct comparative studies, the COMP accepts also evidence derived from indirect efficacy comparisons such as e.g. Matching Adjusted Indirect Comparison (MAIC). While the sponsors comment on the feasibility issue to compare data across trials due to significant trial design and population differences is acknowledged, in the absence of such evidence this requirement is considered as not fulfilled.
- As regards the patients travel burden, the COMP notes that inotersen can be self-administered by the patient or caregiver.
- As regards the burden of monitoring, the COMP took note of section 4.4 of the SmPC for Attrogy/diflunisal, i.e. "Special warnings and precautions for use". In this section the following is noted: *"Attrogy 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 medication, should be carefully monitored."* Additional recommendations for monitoring in this section are as follows: *"Patients treated with NSAIDs long-term, such as diflunisal, should undergo regular medical supervision to monitor for adverse events. Older patients are particularly susceptible to the adverse effects 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."…… 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….. 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*.
- The COMP expects that claims for major contribution to patient care are supported by evidence which shows that a different route of administration (e.g. SC versus oral) translates into a decreased patient burden. Evidence may consist of PRO and QoL data. Patient-experience data with the sponsors product is expected by the COMP. No such data has been submitted for diflunisal.
- The COMP pointed out that efficacy in a broader patient population could in principle also be based on evidence of efficacy in patients in which an authorized product is contraindicated (i.e. 4.3 of the SmPC). This approach was used in the orphan maintenance for vutrisiran where the sponsor has submitted clinical data demonstrating that vutrisiran is efficacious in a subset of patients with moderate-severe renal impairment for whom inotersen is contraindicated. However, no such data has been submitted by the sponsor for diflunisal.

<u>Significant benefit vs patisiran based on major contribution to patient care</u>

The sponsor states that there are no clinical trials directly comparing diflunisal and patisiran, and comparison of data across trials is not feasible due to significant trial design and population differences.

The applicant's claim of significant benefit is made on the grounds that diflunisal offers a major contribution to patient care in comparison to patisiran as it is an oral treatment instead of an intravenous infusion every 3 weeks, as patisiran. This would relieve patients of travel burden. Furthermore, the sponsor emphasizes that administration of patisiran carries a risk of infusion-related reactions (IRRs) and requires premedicated before each administration with intravenous corticosteroid, oral paracetamol and intravenous H1 and H2 blockers.

The sponsor states that diflunisal is administered orally at home and with no premedication requirement, thereby mitigating the need for potentially life-long 3-weekly infusions, significant premedication, potential unpleasant side effects / reactions, as well as frequent travel. The applicant's position is therefore that diflunisal makes a major contribution to patient care and significantly benefits all hATTR-PN patients, regardless of the extent of their disability.

While the COMP considered that these aspects are important and a patient benefit may appear self-evident, the committee concluded the arguments provided by the sponsor are not sufficient to support the significant of diflunisal over patisiran based on MCPC due to the following:

- To be regarded as making a major contribution to patient care, the product should at least be equivalent in terms of efficacy, safety and benefit/risk balance as compared with the authorised medicinal products, reference is made to the Commission notice on the application of Articles 3, 5 and 7 of the EU Orphan Regulation (2016/C 424/03). No data has been provided by the sponsor to support this requirement. In the absence of direct comparative studies, the COMP accepts also evidence derived from indirect efficacy comparisons such as Matching Adjusted Indirect Comparison (MAIC). While the sponsors comment on the feasibility issue to compare data across trials due to significant trial design and population differences is acknowledged, in the absence of such evidence this requirement is considered as not fulfilled.
- While a patient benefit appears self-evident for an oral treatment vs an IV infusion with extensive pre-medication, evidence which demonstrates that the different route of administration translates into a decreased patient burden is still expected. Evidence may consist of PRO and QoL data. Patient-experience data with the sponsors product is expected by the COMP. No such data has been submitted for diflunisal.
- As regards the patients travel burden, the COMP notes that home-administered by a healthcare professional is possible for patisiran, according to the SmPC, i.e. "*Infusion of Onpattro at home may be considered for patients who have tolerated at least 3 infusions well in the clinic. The decision for a patient to receive home infusions should be made after evaluation and recommendation by the treating physician. Home infusions should be performed by a healthcare professional"*.

<u>Significant benefit vs vutrisiran based on major contribution to patient care</u>

The sponsor states that there are no clinical trials directly comparing diflunisal and vutrisiran, and comparison of data across trials is not feasible due to significant trial design and population differences.

The applicant's claim of significant benefit is made on the grounds that diflunisal offers a major contribution to patient care in comparison to vutrisiran as it is a twice daily oral treatment instead of a subcutaneous injection once every 3 months. The sponsor points out that it is mandatory that

injections are administered by a healthcare professional, therefore patients must travel to their clinic for drug administration 4 times annually. This requirement is inconvenient for patients, especially for those with greater disability.

The sponsor also states that use of diflunisal does not require daily oral vitamin A supplementation as is recommended for vutrisiran (4.4 SmPC).

Lastly, the sponsor points out that neither vutrisiran nor diflunisal should be used during pregnancy or when attempting to conceive. However, diflunisal will be cleared from the body within 2-3 days, while vutrisiran is a depot injection which will continue to release therapeutic quantities of drug for 3 months, with normal vitamin A levels not being restored for up to 12 months. According to the sponsor, diflunisal therefore offers greater control (which translates into improved risk mitigation) in comparison to vutrisiran.

The COMP does not consider that the arguments provided by the sponsor are sufficient to support the significant of diflunisal over vutrisiran based on MCPC due to the following:

- To be regarded as making a major contribution to patient care, the product should at least be equivalent in terms of efficacy, safety and benefit/risk balance as compared with the authorised medicinal products, reference is made to the Commission notice on the application of Articles 3, 5 and 7 of the EU Orphan Regulation (2016/C 424/03). No data has been provided by the sponsor to support this requirement. In the absence of direct comparative studies, the COMP accepts also evidence derived from indirect efficacy comparisons such as Matching Adjusted Indirect Comparison (MAIC). While the sponsors comment on the feasibility issue to compare data across trials due to significant trial design and population differences is acknowledged, in the absence of such evidence this requirement is considered as not fulfilled.
- As regards the patients travel burden, the COMP notes that vutrisiran may be self-administered by the patient or caregiver; 4.2 of the SmPC states *"Amvuttra (vutrisiran) may be administered by a healthcare professional, the patient, or a caregiver. Patients or caregivers may inject Amvuttra after guidance has been provided by a healthcare professional on proper subcutaneous injection technique. This medicinal product is ready-to-use and for single-use only".*
- The COMP expects that claims for major contribution to patient care are supported by evidence which shows that a different route of administration (e.g. SC versus oral) translates into a decreased patient burden. Evidence may consist of PRO and QoL data. Patient-experience data with the sponsors product is expected by the COMP. No such data has been submitted for diflunisal.
- The COMP pointed out that efficacy in a broader patient population could in principle also be based on evidence of efficacy in patients in which an authorized product is contraindicated (i.e. 4.3 of the SmPC). This approach was used in the orphan maintenance for vutrisiran where the sponsor has submitted clinical data demonstrating that vutrisiran is efficacious in a subset of patients with moderate-severe renal impairment for whom inotersen is contraindicated. However, no such data has been submitted by the sponsor for diflunisal.
- As regards the sponsor's last point, as the use of both products is not recommended during pregnancy and use of diflunisal is contraindicated (4.3 SmPC) during the third trimester of pregnancy and in breast-feeding (which is not the case for vutrisiran), a major contribution to patient care cannot be established.

<u>Significant benefit vs all gene silencers based on activity on cardiomyopathy disease manifestations</u>

The sponsor states that patients prescribed diflunisal for treatment of hATTR-PN amyloidosis (i.e. on-label) can expect collateral benefits with regard to any cardiac manifestations that they may have. The sponsor makes reference to several studies which show evidence of disease stabilization without significant safety concerns in patients with ATTRwt amyloidosis (i.e., in patients primarily with cardiomyopathy; ATTR-CM) (Lohrmann et al, 2020; Sekijima et al, 2015; Ikram et al, 2018; Wixner et al, 2019; Castano et al, 2012; Takahashi et al, 2014; Berk et al, 2013; Koyama et al, 2015; Rosenblum et al, 2018; Siddiqi et al, 2022).

The COMP does not consider this evidence as sufficient to support the significant benefit over authorized TTR silencer therapies. The COMP also took note of the CHMP assessment report which states that "*Given that there is no dedicated study on a potential dose-response relationship of diflunisal in the prolongation of QT interval and that ATTR can have a cardiomyopathy variant that can lead to electrophysiological changes the applicant has included in section 4.4 a reference regarding treatment of patients with prolonged QT interval along with the other proposed cardiac conditions".* Furthermore, heart (cardiac) failure is a common (may affect up to 1 in 10 people) side effect, according to 4.8 of the SmPC. Severe heart failure is a contraindication for use of diflunisal (4.3 SmPC). Under 4.4 of the SmPC it is stated that "*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*)."

The sponsor points out that the safety information in the SmPC is based primarily on historic use of diflunisal as an NSAID rather than on observed adverse reaction frequencies in the indication approved for Attrogy. The dose to be used in the ATTR-FAP indication is lower than that routinely used historically for NSAID indications (250 mg twice daily for ATTR-FAP vs 500 mg twice daily for NSAID indications).

In conclusion, the COMP does not consider that the data presented by the sponsor is sufficient to support the significant benefit of diflunisal over the three authorized satisfactory methods inotersen, patisiran and vutrisiran. The recently authorized eplontersen is also considered a satisfactory method and the significant benefit of diflunisal vis a vis this product also needs to be established by the sponsor. Accordingly, the COMP adopted a list of questions on significant benefit.

4. COMP list of issues

Prevalence

The prevalence should be estimated for the whole condition, which includes patients with wild-type ATTR-amyloidosis cardiomyopathy. The epidemiology of ATTR amyloidosis is currently changing rapidly.

For the estimation and presentation of the prevalence estimate the sponsor is advised to refer to the "*Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation*". The sponsor should justify the inclusion and choice of sources selected for the prevalence estimation and describe the methodology used for these calculations. Due to significant uncertainties surrounding many of the underlying assumptions, the sponsor should elaborate on the prevalence estimate for the proposed orphan condition and is asked to comment on the accurate reflection of current developments (e.g. increasing use of scintigraphy and ageing population).

Significant benefit

The COMP does not consider that the data presented by the sponsor is sufficient to support the significant benefit of diflunisal over the three authorized satisfactory methods inotersen, patisiran and vutrisiran.

The recently authorized eplontersen is also considered a satisfactory method and the significant benefit of diflunisal vis a vis this product also needs to be established by the sponsor.

Additional justification is requested on support of the major contribution to patient care (MCPC) claim:

a) for a major contribution to patient care, the product should at least be equivalent in terms of efficacy, safety and benefit/risk balance as compared with the satisfactory methods mentioned above. In the absence of direct comparative studies, the COMP accepts also evidence derived from indirect efficacy comparisons such as Matching Adjusted Indirect Comparison (MAIC).

b) Furthermore, the COMP expects that claims for major contribution to patient care are substantiated by evidence which shows that a different route of administration (oral versus SC or IV) translates into a decreased patient burden. Evidence may consist of patient reported outcome (PRO) and quality of life (QoL) data.