**OPINION ON
MEDICINAL
PRODUCTS**

vutrisiran

AMVUTTRA 25 mg,

solution for injection in prefilled syringe

First assessment

Adopted by the Transparency Committee on 14 December 2022

SUMMARY

The legally binding text is the original French opinion version

Key points

Approval of reimbursement for the treatment of hereditary transthyretin amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.

Therapeutic improvement?

No therapeutic improvement with respect to ONPATTRO (patisiran).

Role in therapeutic strategy?

Patients with hATTR amyloidosis with polyneuropathy require specialist care with regular follow-up by a multidisciplinary team (particularly including a neurologist, a cardiologist, and a geneticist). The treatment decision must be taken in coordination with FILMENUS network neuromuscular disease expert/reference centres.

The treatment of hATTR amyloidosis with polyneuropathy is currently based on:

- Symptomatic treatments of clinical manifestations of the disease (such as neurological, digestive, cardiac and ophthalmological manifestations) along with treatments of end-stage organ damage (such as end-stage heart or kidney failure);
- Specific anti-amyloid treatments for symptomatic patients.

Anti-amyloid treatments target the cause of the disease by preventing the formation of new amyloid deposits. To date, 3 anti-amyloid medicinal products have been granted marketing authorisation for the treatment of hATTR amyloidosis with polyneuropathy:

- ONPATTRO (patisiran), intravenous infusion: interfering RNA indicated for patients with stage 1 and 2 polyneuropathy.
- TEGSEDI (inotersen), subcutaneous injection once per week: antisense oligonucleotide indicated for stage 1 and 2 polyneuropathy in patients with hATTR amyloidosis.
- VYNDAQEL (tafamidis), per os: tetramer stabiliser indicated for patients with stage 1 polyneuropathy only.

Liver transplantation **Erreur ! Signet non défini.** is a therapeutic option, for early-onset forms (< 50 years) with V30M mutation. Patients must have an estimated 5-year survival < 50% to benefit. The prognostic factors of poorer response to liver transplantation are late-onset forms (> 50 years), treatment at an advanced stage of the disease or poor nutritional status of patients. **Erreur ! Signet non défini.**, **Erreur ! Signet non défini.** The aim of liver transplantation is to prevent new amyloid deposits by suppressing the main source of mutated TTR.

Despite transplantation, some patients may continue to experience progression insofar as it does not prevent mutated TTR production in the eye or wild-type TTR production in non-V30M or older V30M patients; this may contribute to the progression of clinical neurological, ocular and cardiac manifestations, even post-transplantation.

Role of the medicinal product

Considering the lack of evidence of superiority of vutrisiran over patisiran, but only evidence of non-inferiority of vutrisiran versus patisiran on a biological ranked secondary outcome measure and the effect size of vutrisiran based on the evidence of superiority versus an external placebo group on the mean variation of the mNIS+7 score after 18 months of treatment outcome measure, in an open-label study, the proprietary medicinal product AMVUTTRA (vutrisiran) is a second-intent treatment, after the proprietary medicinal product ONPATTRO (patisiran) which remains the first-intent treatment, for the treatment of adult patients with hATTR amyloidosis with stage 1 or stage 2 polyneuropathy.

In the absence of comparative clinical studies versus other clinically relevant comparators, it is not possible to rank AMVUTTRA (vutrisiran) versus these drugs.

Committee's conclusions

Clinical Benefit

- ➔ Hereditary transthyretin amyloidosis with stage 1 or 2 polyneuropathy is a rare, serious, incapacitating disease with fatal outcomes.
- ➔ The proprietary medicinal product AMVUTTRA (vutrisiran) is a preventive treatment.
- ➔ The efficacy/adverse effect ratio is significant.
- ➔ Therapeutic alternatives are available.
- ➔ AMVUTTRA (vutrisiran) is a second-intent treatment, after ONPATTRO (patisiran) which remains the first-intent treatment, for adult patients with hATTR amyloidosis with stage 1 or stage 2 polyneuropathy.

➔ Public health benefit

Considering:

- the severity of the disease and its prevalence,
- the identified medical need for well-tolerated, effective therapeutic alternatives, promoting compliance,
- the partial response to the identified need on account of:
- the lack of expected additional impact on morbidity-mortality;
- an expected favourable impact on quality of life of vutrisiran versus the external placebo group via the NORFOLK QOF DN self-questionnaire which was a ranked secondary outcome measure, the open-label nature of the study however reducing the impact of this finding,
- an expected impact on delivery of care, versus the alternatives available, particularly ONPATTRO (patisiran) and TEGSEDI (inotersen), considering the subcutaneous method of administration of AMVUTTRA (vutrisiran) every 3 months,

AMVUTTRA (vutrisiran) is likely to have an additional impact on public health.

Considering all of these elements, the Committee deems that the actual clinical benefit of AMVUTTRA (vutrisiran) is significant in the marketing authorisation indication.

The Committee approves inclusion in the list of proprietary medicinal products qualifying for reimbursement under social security and in the list of proprietary products approved for community use for the indication and at the dosages of the marketing authorisation.

Recommended reimbursement rate: 65%

Clinical Added Value

Considering:

- the evidence of the superiority of vutrisiran versus an external placebo group from the APOLLO study (pivotal study of patisiran) in terms of mNIS+7 score improvement, as well as on ranked secondary outcome measures, in an open-label phase III study, HELIOS-A,
- the differences observed in respect of certain patient characteristics between the vutrisiran and external placebo groups and the lack of randomisation between these 2 groups, preventing comparability of the groups,
- the evidence of non-inferiority of vutrisiran versus patisiran, only on a biological ranked secondary outcome measure, in the HELIOS-A open-label phase III study, failing to establish added value of vutrisiran over patisiran,
- the methodology of the HELIOS-A study which hence appears to be non-robust, which reduces the impact of its findings,

but also considering:

- the three-monthly subcutaneous administration of vutrisiran enabling convenience of use compared to the alternatives available, with an expected impact on the care pathway, but with a lack of supporting data,
- the safety profile of vutrisiran which appears to be favourable with a follow-up period limited to 18 months of treatment,

the Committee deems that the proprietary medicinal product AMVUTTRA (vutrisiran) provides no clinical added value (CAV V) versus ONPATTRO (patisiran), for the treatment of adult patients with hATTR amyloidosis with stage 1 or 2 polyneuropathy.