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Public summary of opinion on orphan designation

3-(3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorobenzoic acid for the treatment of ATTR amyloidosis

On 19 November 2018, orphan designation (EU/3/18/2081) was granted by the European Commission to Pharma Gateway AB, Sweden, for 3-(3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorobenzoic acid (also known as AG10) for the treatment of ATTR amyloidosis.

What is ATTR amyloidosis?

ATTR amyloidosis or transthyretin-mediated amyloidosis belongs to a group of diseases called systemic amyloidosis in which deposits of proteins (called amyloids) accumulate and cause damage in body organs. In ATTR amyloidosis, the amyloids are made up of an abnormal form of transthyretin, a protein produced in the liver that transports various substances in the blood.

In patients with ATTR amyloidosis, the amyloids accumulate mainly in the heart and the nervous system. Patient with this condition usually have heart problems and symptoms such as muscle weakness in the limbs and, at later stages, inability to walk, problems affecting the stomach and the gut (leading to malnutrition), and bladder dysfunction.

ATTR amyloidosis is a long-term debilitating disease due to the progressive worsening of nervous system symptoms. It is also life threatening because amyloid deposits in the heart can cause fatal heart conditions.

What is the estimated number of patients affected by the condition?

At the time of designation, ATTR amyloidosis affected approximately 0.1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 5,000 people[*], and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

[*]Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed on the basis of data from the European Union (EU 28), Norway, Iceland and Liechtenstein. This represents a population of 517,400,000 (Eurostat 2018).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

What treatments are available?

At the time of designation, the medicines Vyndaqel (tafamidis), Tegsedi (inotersen) and Onpattro (patirisan) were authorised in the EU to treat ATTR amyloidosis in patients with the early stages of nerve disease. The only other treatment option was liver transplantation.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with ATTR amyloidosis because early results suggest that it can be of value in patients with heart problems, whereas existing treatments are authorised for patients with symptoms affecting the nervous system. This assumption will need to be confirmed at the time of marketing authorisation, in order to maintain the orphan status.

How is this medicine expected to work?

This medicine acts as a stabilizer of transthyretin, the protein that makes up the amyloids in patients with ATTR amyloidosis. After being taken by mouth it attaches to transthyretin in the blood, which prevents the abnormal protein from breaking up and forming amyloids. This is expected to slow down the progression of the disease.

What is the stage of development of this medicine?

The effects of the medicine have been evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials with the medicine in patients with ATTR amyloidosis were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for ATTR amyloidosis or designated as an orphan medicinal product elsewhere for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 11 October 2018 recommending the granting of this designation.

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Opinions on orphan medicinal product designations are based on the following three criteria:

- the seriousness of the condition;
- the existence of alternative methods of diagnosis, prevention or treatment;
- either the rarity of the condition (affecting not more than 5 in 10,000 people in the EU) or insufficient returns on investment.

Designated orphan medicinal products are products that are still under investigation and are considered for orphan designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of quality, safety and efficacy is necessary before a product can be granted a marketing authorisation.

For more information

Sponsor's contact details:

Contact details of the current sponsor for this orphan designation can be found on EMA website, on the medicine's rare disease designations page.

For contact details of patients' organisations whose activities are targeted at rare diseases see:

- Orphanet, a database containing information on rare diseases, which includes a directory of patients' organisations registered in Europe;
- European Organisation for Rare Diseases (EURORDIS), a non-governmental alliance of patient organisations and individuals active in the field of rare diseases.

Translations of the active ingredient and indication in all official EU languages[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	3-(3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorobenzoic acid	Treatment of ATTR amyloidosis
Bulgarian	3-(3-(3,5-диметил-1H-пиразол-4-ил)пропокси)-4-флуоробензоена киселина	Лечение на транстиретинова амилоидоза
Croatian	3-(3-(3,5-dimetil-1H-pirazol-4-il)propoksi)-4-fluorobenzoična kiselina	Liječenje ATTR amiloidoze
Czech	kyselina 3-(3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorbenzoová	Léčba ATTR amyloidózy
Danish	3-(3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorbenzoesyre	Behandling af familiær ATTR amyloidose
Dutch	3-(3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorbenzoëzuur	Behandeling van ATTR amyloïdose
Estonian	3-(3-(3,5-dimetüül-1H-pürasool-4-üül)propoksü)-4-fluorobensoehape	Transtüretiiniga seotud amüloidoosi (ATTR) ravi
Finnish	3-(3-(3,5-dimetyyli-1H-pyratsoli-4-yyli)propoksi)-4-fluoribentsoehappo	Suvuittain esiintyvän amyloidipolyneuropatian hoito
French	Acide 3-[3-(3,5-diméthyl-1H-pyrazol-4-yl)propoxy]-4-fluorobenzoïque	Traitement de l'amyloïdose ATTR
German	3-[3-(3,5-Dimethyl-1H-pyrazol-4-yl)propoxy]-4-fluorbenzoesäure	Behandlung der ATTR Amyloidose
Greek	3-(3-(3,5-διμεθυλο-1H-πυραζολ-4-υλ)προποξυ)-4-φθοροβενζοϊκό οξύ	Θεραπεία της ATTR αμυλοείδωσης
Hungarian	3-(3-(3,5-dimetil-1H-pirazol-4-il)propoxi)-4-fluorbenzoesav	ATTR típusú amyloidosis kezelése
Italian	3-(3-(3,5-dimetil-1H-pirazol-4-il)propossi)-4-acido fluorobenzoico	Trattamento della Amiloidosi familiare (ATTR)
Latvian	3-(3-(3,5-dimetil-1H-pirazol-4-il)propoksi)-4-fluorbenzoskābe	ATTR amiloidozes ārstēšana
Lithuanian	3-(3-(3,5-dimetil-1H-pirazol-4-il)propoksi)-4-fluorobenzenkarboksirūgštis	ATTR amiloidozės gydymas
Maltese	3-(3-(3,5-dimetil-1H-pirażol-4-yl)propossi)-4-aċidu fluworobenzoiċ	Kura tal-amilojdosi assoċjata mat-*transthyretin* (ATTR)
Polish	Kwas 3-(3-(3,5-dimetylo-1H-pirazolo-4-yl)propoksy)-4-fluorobenzoesowy	Leczenie amyloidozy wrodzonej typu ATTR
Portuguese	Ácido 3-(3-(3,5-dimetil-1H-pirazol-4-il) propoxi)-4-fluorobenzóico	Tratamento da amiloidose associada à transtirretina
Romanian	Acid 3-(3-(3,5-dimetil-1H-pirazol-4-il)propoxi)-4-fluorbenzoic	Tratamentul amiloidozei cu transtiretina (ATTR)
Slovak	Kyselina 3-(3-(3,5-dimetyl-1H-pyrazol-4-yl)propoxy)-4-fluórobenzoová	Liečba ATTR amyloidózy

[1] At the time of designation

Slovenian	3-(3-(3,5-dimetil-1H-pirazol-4-il)propoksi)-4-fluorobenzojska kislina	Zdravljenje amiloidne transtiretinske amiloidoze
Spanish	Ácido 3-(3-(3,5-dimetil-1H-pirazol-4-il)propoxi)-4-fluorobenzoico	Tratamiento de amiloidose associada a la transtirretina
Swedish	3-(3-(3,5-dimetyl-1H-pyrazol-4-yl)propoxi)-4-fluorbensoesyra	Behandling av ATTR amyloidos
Norwegian	3-(3-(3,5-dimetyl-1H-pyrazol-4-yl)propoksy)-4-fluorbenzosyre	Behandling av ATTR amyloidose
Icelandic	3-(3-(3,5-dímetýl-1H-pýrasól-4-yl)própoxý)-4-flúorbensósýra	Meðferð við ATTR mýlildisfjöltaugakvilla