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Public summary of opinion on orphan designation

2-(hydroxymethyl)-2-(methoxymethyl)-1-azabicyclo[2.2.2]octan-3-one for the treatment of myelodysplastic syndromes

On 25 July 2019, orphan designation EU/3/19/2180 was granted by the European Commission to Aprea Therapeutics AB, Sweden, for 2-(hydroxymethyl)-2-(methoxymethyl)-1-azabicyclo[2.2.2]octan-3-one (also known as APR-246) for the treatment of myelodysplastic syndromes.

What are myelodysplastic syndromes?

Myelodysplastic syndromes are a group of disorders in which the red blood cells, white blood cells and platelets produced by the bone marrow (the spongy tissue inside large bones) do not mature normally. Patients with myelodysplastic syndromes can develop tiredness or weakness due to anaemia (low red blood cell counts), infections due to low white blood cell counts, and bruising or abnormal bleeding due to low platelet counts.

Myelodysplastic syndromes are long-term debilitating and life-threatening diseases because they can lead to severe anaemia, infections or bleeding, and can result in leukaemia (cancer of the white blood cells).

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

At the time of designation, myelodysplastic syndromes affected less than 2 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 104,000 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).

What treatments are available?

At the time of designation, several medicines were authorised in the EU for the treatment of myelodysplastic syndromes including azacitidine, lenalidomide and imatinib. The choice of treatment depended on a number of factors, including the type and the extent of the disease, whether it had

*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 518,400,000 (Eurostat 2019).

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been treated before, and the patient's age, symptoms and general state of health. The main treatments included medicines that stimulate production of blood cells, chemotherapy (medicines to treat cancer), blood transfusions and stem cell transplantation. Stem cell transplantation is a procedure where the patient's bone marrow is cleared of cells and replaced with stem cells from a donor to form new bone marrow that produces healthy blood cells.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with myelodysplastic syndromes. Laboratory data showed that the medicine can be more effective than azacitidine at slowing down the growth of tumours. Early data in patients also suggested that treatment with the medicine in combination with azacitidine may be more effective than other treatments.

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?

The medicine is expected to affect a protein called p53, which is involved in cell death; p53 has an abnormal shape in some patients with myelodysplastic syndromes and loses its ability to induce the death of cancer cells. By stabilising the abnormal p53 protein, this medicine is expected to restore its ability to cause death of cancer cells, slowing down the progression of the condition.

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 myelodysplastic syndromes were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of myelodysplastic syndromes. Orphan designation of the medicine had been granted in the United States for this condition.

In accordance with Regulation (EC) No 141/2000, the COMP adopted a positive opinion on 20 June 2019, recommending the granting of this designation.

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.

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	2-(hydroxymethyl)-2-(methoxymethyl)-1-azabicyclo[2.2.2]octan-3-one	Treatment of myelodysplastic syndromes
Bulgarian	2-(хидроксиметил)-2-(метоксиметил)-1 азабицикло[2.2.2]октан-3-он	Лечение на миелодиспластичен синдром
Croatian	2-metoksimetil-2-hidroksimetil-1-azabiciklo[2,2,2]oktan-3-on	Liječenje mijelodisplastičnih sindroma
Czech	2-hydroxymethyl-2-methoxymethyl-1-azabicyklo[2,2,2]oktan-3-on	Léčba myelodysplastického syndromu
Danish	2-methoxymethyl-2-hydroxymethyl-1-azabicyclo[2,2,2]octan-3-on	Behandling af myelodysplastiske syndromer
Dutch	2-methoxymethyl-2-hydroxymethyl-1-azabicyclo[2,2,2]octan-3-on	Behandeling van myelodysplastische syndromen
Estonian	2-hüdroksümetüül-2-metoksümetüül-1-asabitsüklo[2,2,2]oktaan-3-oon	Müelodüsplastiliste sündroomide ravi
Finnish	2-metoksimetyyli-2-hydroksimetyyli-1-atsabisyklo[2.2.2]oktan-3-oni	Myelodysplastisten syndroomien hoito
French	2-(hydroxyméthyl)-2-(méthoxyméthyl)-1-azabicyclo[2.2.2]octan-3-one	Traitement des syndromes myélodysplasiques
German	2-methoxymethyl-2-hydroxymethyl-1-azabicyclo[2.2.2]octan-3-on	Behandlung der myelodysplastischen Syndrome
Greek	2-μεθοξυμεθυλο-2-υδροξυμεθυλο-1-αζαδικυκλο[2,2,2]οκταν-3-όνη	Θεραπεία των μυελοδυσπλαστικών συνδρόμων
Hungarian	2-metoximetil-2-hidroximetil-1-azabiciklo[2,2,2]oktán-3-on	Myelodysplasias syndroma kezelése
Italian	2-metossimetil-2-idrossimetil-1-azabiciclo[2.2.2]ottan-3-one	Trattamento delle sindromi mielodisplastiche
Latvian	2-(hidroksimetil)-2-(oksimetil)-1-azabiciklo[2,2,2]oktān-3-ons	Mielodisplastisko sindromu ārstēšana
Lithuanian	2-hidroksimetil-2-metoksimetil-1-azabiciklo[2,2,2]oktan-3-onas	Mielodisplastinių sindromų gydymas
Maltese	2-(idrossimetil)-2-(metossimetil)-1-ażabiċiklo[2,2,2]oktan-3-on	Kura tas-sindromi mjelodisplastiċi
Polish	2-metoksymetylo-2-hydroksymetylo-1-azabicyklo[2,2,2]oktan-3-on	Leczenie zespołów mielodysplastycznych
Portuguese	2-metoximetil-2-hidroximetil-1-azabiciclo[2.2.2]-3-octanona	Tratamento dos síndromes mielodisplásicos
Romanian	2-(hidroximetil)-2-(metoximetil)-1-azabiciclo[2.2.2]octan-3-onă	Tratamentul sindromului mielodisplazic

[1] At the time of designation

Language	Active ingredient	Indication
Slovak	2-metoxymetyl-2-hydroxymetyl-1-azabicyklo[2,2,2]oktán-3-ón	Liečba myelodysplastického syndrómu
Slovenian	2-metoksimetil-2-hidroksimetil-1-azabiciklo[2,2,2]oktan-3-on	Zdravljenje mielodisplastičnega sindroma
Spanish	2-metoximetil-2-hidroximetil-1-azabiciclo[2,2,2]octan-3-ona	Tratamiento de los síndromes mielodisplásicos
Swedish	2-metoximetyl-2-hydroximetyl-1-azabicyklo[2,2,2]oktan-3-on	Behandling av myelodysplastiska syndrom
Norwegian	2-metoksymetyl-2-hydroksymetyl-1-azabisyklo[2.2.2]oktan-3-on	Behandling av myelodysplastisk syndrom
Icelandic	2-metoxýmetýl-2-hýdroxýmetýl-1-azabísýkló[2.2.2]oktan-3-ón	Til meðferðar við mergmisþroskaheilkenni