



European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR ORPHAN MEDICINAL PRODUCTS

PUBLIC SUMMARY OF POSITIVE OPINION FOR ORPHAN DESIGNATION OF ribonucleotide reductase R2 specific phosphorothioate oligonucleotide for the treatment of acute myeloid leukaemia.

On 8 May 2008, orphan designation (EU/3/08/542) was granted by the European Commission to Dr Ulrich Granzer, Germany, for ribonucleotide reductase R2 specific phosphorothioate oligonucleotide for the treatment of acute myeloid leukemia.

What is acute myeloid leukaemia?

Acute myeloid leukaemia is a disease in which cancer cells are found in the blood and the bone marrow. The bone marrow is the spongy tissue inside the large bones in the body. Normally, the bone marrow makes cells called “blasts”, which mature into several different types of blood cells that have specific functions in the body. These include red cells, white cells and platelets. Red blood cells carry oxygen and other materials to all tissues of the body. White blood cells fight infection. Platelets make the blood clot. When leukaemia develops, the bone marrow produces large numbers of abnormal blood cells. There are several types of leukaemias. In myeloid leukaemia, immature cells called blasts that should develop into a type of white blood cells called granulocytes are affected. The blasts do not mature, and become too many. These blast cell are then found in the blood; they also accumulate in the bone marrow where they take the place of the other types of normal blood cells, causing anaemia, easy bruising, and frequent infections. Myeloid leukaemia can be acute, when it develops quickly with many blasts. Acute myeloid leukaemia is life-threatening.

What are the methods of treatment?

Treatment for leukaemia is complex, and depends on a number of factors including the type of leukaemia, the extent of the disease and whether the leukaemia has been treated before. It also depends on the age, the symptoms, and the general health of the patient. The primary treatment of acute myeloid leukaemia is chemotherapy (using drugs to kill cancer cells). Several products were authorised for the condition in the Community at the time of submission of the application for orphan drug designation. Satisfactory argumentation has been submitted by the sponsor to justify the assumption that ribonucleotide reductase R2 specific phosphorothioate oligonucleotide might be of potential significant benefit for the treatment of acute myeloid leukaemia because of its mechanism of action which is different from current treatments. This assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

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

Based on the information provided by the sponsor and previous knowledge of the Committee, acute myeloid leukaemia was considered to affect less than 2.4 in 10,000 persons in the European Union, which, at the time of designation, corresponded to about 120,000 persons.

* Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed based on data from the European Union (EU 27), Norway, Iceland and Lichtenstein. This represents a population of 502,282,000 (Eurostat 2008). This estimate is based on available information and calculations presented by the sponsor at the time of the application.

How is this medicinal product expected to act?

When a cell is dividing into two, the genetic material in cells is copied so that the resulting cells have the same genetic information as the original cell. This process involves enzymes (proteins that speed up the conversion of certain substances into other substances) that have specific roles in the process. One of these enzymes is called ribonucleotide reductase. This enzyme is responsible for the production of substances necessary for copying of the genetic material. Ribonucleotide reductase has two parts, called R1 and R2. If this enzyme does not work well, cell division will stop. As rapidly dividing tumour cells have a high activity of this enzyme, inhibition of ribonucleotide reductase production with ribonucleotide reductase R2 specific phosphorothioate oligonucleotide is thought to stop the division of tumour cells.

What is the stage of development of this medicinal product?

At the time of submission of the application for orphan designation, clinical trials in patients with acute myeloid leukaemia were initiated.

Ribonucleotide reductase R2 specific phosphorothioate oligonucleotide was not authorised anywhere worldwide for acute myeloid leukaemia, at the time of submission. Orphan designation of ribonucleotide reductase R2 specific phosphorothioate oligonucleotide was granted in the United States for the condition.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 4 March 2008 a positive opinion recommending the grant of the above-mentioned designation.

Opinions on orphan medicinal products designations are based on the following cumulative criteria: (i) the seriousness of the condition, (ii) the existence or not of alternative methods of diagnosis, prevention or treatment and (iii) either the rarity of the condition (considered to affect not more than five in ten thousand persons in the Community) or the insufficient return of development investments.

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

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**Translations of the active ingredient and indication in all EU languages
and Norwegian and Icelandic**

Language	Active Ingredient	Indication
English	Ribonucleotide reductase R2 specific phosphorothioate oligonucleotide	Treatment of acute myeloid leukaemia
Bulgarian	Рибонуклеотид редуктаза R2 специфичен фосфоротиоат олигонуклеотид	Лечение на остра миелоидна левкемия
Czech	Pro ribonukleotid reduktázu R2 specifický fosforothioát oligonukleotid	Léčba akutní myeloidní leukémie
Danish	Ribonukleotidreduktase R2 specifik phosphorothioat- oligonukleotid	Behandling af akut myeloid leukæmi
Dutch	Ribonucleotidereductase R2-specifieke fosforothioaat-oligonucleotide	Behandeling van acute myeloïde leukemie
Estonian	Ribonukleotiidreduktaas-R2-spetsiifiline fosforotioaat-oligonukleotiid	Akuutse müeloidse leukeemia ravi
Finnish	Ribonukleotidireduktaasi R2 -spesifinen fosforotioaatti-oligonukleotidi	Akuutin myelooisen leukemian hoito
French	Oligonucléotide phosphorothioate spécifique de l'unité R2 de la ribonucléotide réductase	Traitement de la leucémie aiguë myéloïde
German	Ribonukleotid Reduktase R2-spezifisches Phosphorothioat-Oligonukleotid	Behandlung der akuten myeloischen Leukämie
Greek	Ειδικό θειοφωσφορικό ολιγονουκλεοτίδιο αναγωγής ριβονουκλεοτιδίου R2	Θεραπεία της οξείας μυελοειδούς λευχαιμίας
Hungarian	Ribonukleotid-reduktáz R2 specifikus foszfor-tioát oligonukleotid	Akut myeloid leukaemia kezelése
Italian	Oligonucleotide fosforotioato specifico per la ribonucleotide reduttasi R2	Trattamento della leucemia mieloide acuta
Latvian	Fosfortioāta oligonukleotīda specifiskā ribonukleotīdreduktāze R2	Akūtas mieloleikozes ārstēšana
Lithuanian	Ribonukleotido reduktazės R2 specifinis fosforotioato oligonukleotidas	Ūmios mieloleukozės gydymas
Maltese	Oligonukleotide phosphothioate speċifiku għall-parti R2 tar-ribonukleotide reductase	Kura tal-lewkimja mjelojda akuta
Polish	Oligonukleotyd fosforylowany swoisty dla reduktazy rybonukleotydu R2	Leczenie ostrej białaczki szpikowej
Portuguese	Oligonucleótido fosforotioato específico da ribonucleótido reductase R2	Tratamento da leucemia mielóide aguda
Romanian	Oligonucleotidă fosforotioat cu specificitate pentru ribonucleotid-reductaza R2	Tratamentul leucemiei mieloide acute
Slovak	Pre ribonukleotid reduktázu R2 špecifický fosforotioát oligonukleotid	Liečba akútnej myeloickej leukémie
Slovenian	Za ribonukleotid-reduktazo R2 specifični fosforotioat oligonukleotid	Zdravljenje akutne mieloične levkemije
Spanish	Oligonucleótido fosforotioato específico para la ribonucleótido reductasa R2	Tratamiento de la leucemia mieloide aguda
Swedish	Fosforotioat-oligonukleotid specifik för ribonukleotidreduktas R2	Behandling av akut myeloisk leukemi

Norwegian	Ribonukleotidreduktase R2-spesifikk fosforotioat-oligonukleotid	Behandling av akutt myelogen leukemi
Icelandic	Ríbónúkleótíð-redúktasa-R2 sértækt fosfórótíóat-ólígónúkleótíð	Meðferð við bráðu kyrningahvítblæði