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 NGR-human tumour necrosis factor for the treatment of hepatocellular carcinoma

On 9 November 2009, orphan designation (EU/3/09/686) was granted by the European Commission to MolMed S.p.A., Italy, for NGR-human tumour necrosis factor for the treatment of hepatocellular carcinoma.

What is hepatocellular carcinoma?
Hepatocellular carcinoma is a primary cancer of the liver (a cancer that starts in the liver, rather than a cancer that has spread to the liver from another location in the body). It is more common in men than in women, and occurs mostly in people who have scarring of the liver (cirrhosis) or after infection with the hepatitis B or C viruses. Symptoms of the disease include pain and swelling in the tummy, weight loss, weakness, loss of appetite and nausea (feeling sick).
Hepatocellular carcinoma is a severe and life-threatening disease that leads to very poor long-term survival.

What is the estimated number of patients affected by the condition?
At the time of designation, hepatocellular carcinoma affected approximately 1 in 10,000 people in the European Union (EU)[*]. This is equivalent to a total of around 50,000 people, and is below the threshold for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and 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 hepatocellular carcinoma. The choice of treatment depended mainly on how advanced the disease is. Surgery to remove the tumour and liver transplantation were the only chances of cure, but could only be used in very few patients. Other treatments included radiotherapy (treatment with radiation), chemotherapy (medicines to treat cancer) and immunotherapy (treatment by stimulation of the immune system, the body's natural defences).
The sponsor has provided sufficient information to show that NGR-human tumour necrosis factor might be of significant benefit for patients with hepatocellular carcinoma because early studies indicate that it might improve the treatment of patients with this condition. 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?
NGR-human tumour necrosis factor consists of two parts, NGR and human tumour necrosis factor:

[*]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 27), Norway, Iceland and Liechtenstein. This represents a population of 504,800,000 (Eurostat 2009).

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- NGR is a protein that attaches to a receptor called CD13, which is found on the surface of the cells lining the new blood vessels that form around tumours;
- human tumour necrosis factor is a protein that can kill these cells.

Because it is attached to NGR, the cell-killing activity of tumour necrosis factor is concentrated at the cells lining the blood vessels that formed around tumours. This combined effect results in damage to blood vessels supplying a tumour, reducing its supply of oxygen and nutrients and leading to the tumour dying back.

What is the stage of development of this medicine?

The effects of NGR-human tumour necrosis factor have been evaluated in experimental models.
At the time of submission of the application for orphan designation, clinical trials in patients with hepatocellular carcinoma were ongoing.
At the time of submission, NGR-human tumour necrosis factor was not authorised anywhere in the EU for hepatocellular carcinoma or designated as 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 2 September 2009 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 Community) 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.

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

Language	Active ingredient	Indication
English	NGR-human tumour necrosis factor	Treatment of hepatocellular carcinoma
Bulgarian	NGR-човешки тумор некротизиращ фактор	Лечение на хепатоцелуларен карцином
Czech	NGR-lidský faktor nekrotizující nádory	Léčba hepatocelulárního karcinomu
Danish	NGR human tumor nekrosefaktor	Behandling af hepatocellulært carcinom
Dutch	NGR-humaan tumornecrosefactor	Behandeling van hepatocellulair carcinoom
Estonian	Inimese NRG tuumori nekroosi faktor	Hepatotsellulaarse kartsinoomi ravi
Finnish	Ihmisen NGR-tuumorinekroositekijä	Hepatosellulaarisen karsinooman hoito
French	NGR facteur humain de nécrose tumorale	Traitement du carcinome hépatocellulaire
German	NGRhumaner Tumornekrosefaktor	Behandlung des Leberzellkarzinoms
Greek	NGR-ανθρώπινος παράγοντας νέκρωσης όγκων	Θεραπεία του ηπατοκυταρρικού καρκινώματος
Hungarian	NGR humán tumornekrózis faktor	Hepatocelluláris carcinoma kezelése
Italian	NGR-fattore umano di necrosi tumorale	Trattamento del carcinoma epatocellulare
Latvian	NGR-cilvēka tumora nekrozes faktors	Hepatocellulāras karcinomas ārstēšana
Lithuanian	NGR-žmogaus navikų nekrozės faktorius	Hepatoceliulinės karcinomos gydymas
Maltese	NGR fattur uman tan-nekrosi tat-tumur	Kura tal-karċinoma epatoċellulari
Polish	Sprzężony z NGR ludzki czynnik martwiczy nowotworu	Leczenie raka wątrobowokomórkowego
Portuguese	NGR-factor de necrose tumoral humano	Tratamento do carcinoma hepatocelular
Romanian	NGR-factor uman de necroză tumorală	Tratamentul carcinomului hepatocelular
Slovak	NGR-ľudský faktor nekrotizujúci nádory	Liečba hepatocelulárneho karcinómu
Slovenian	NGR - tumorje nekrotizirajoči faktor pri ljudeh	Zdravljenje hepatocelularnega karcinoma
Spanish	NGR - factor de necrosis tumoral humano	Tratamiento del carcinoma hepatocelular
Swedish	NGR-human tumörnekrosfaktor	Behandling av hepatocellulärt karcinom
Norwegian	NGR-human tumornekrosefaktor	Behandling av hepatocellulært karsinom
Icelandic	Manna NGR-æxlisdrepsþáttur	Meðferð við lifrarfrumukrabbameini