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Ultomiris (*ravulizumab*)

An overview of Ultomiris and why it is authorised in the EU

What is Ultomiris and what is it used for?

Ultomiris is a medicine used to treat:

- adults and children weighing at least 10 kg who have paroxysmal nocturnal haemoglobinuria (PNH), a disease in which the immune system attacks and damages red blood cells, resulting in anaemia (low red blood cell counts), thrombosis (blood clots in the blood vessels), pancytopenia (low counts of blood cells) and dark urine;
- adults and children weighing at least 10 kg who have atypical haemolytic uraemic syndrome (aHUS), a disease in which the immune system causes damage leading to anaemia, thrombocytopenia (a decrease in the number of platelets, components that help the blood to clot) and kidney failure;
- adults with generalised myasthenia gravis (gMG), a disease in which the immune system attacks and damages receptors at the junction between nerves and muscle cells, causing muscle weakness and tiredness;
- adults with neuromyelitis optica spectrum disorders (NMOSD), inflammatory disorders that affect mainly the optic nerve (which connects the eye to the brain) and the spinal cord. This leads to impaired vision, loss of sensation, loss of bladder control, weakness and paralysis of the arms and legs.

In PNH, Ultomiris is used in patients who have symptoms indicating high disease activity or who have been treated with eculizumab (another medicine for PNH and aHUS) for at least the past 6 months and have evidence that the treatment is working.

In aHUS, Ultomiris is used in patients who either have not received complement inhibitors (such as eculizumab) before or who have received eculizumab for at least 3 months and have evidence that the treatment is working.

In gMG, Ultomiris is given with other medicines in patients whose immune system produces a specific antibody (type of protein) against a target found on muscle cells, called acetylcholine receptor.

In NMOSD, Ultomiris is used in patients who have antibodies against a protein called aquaporin-4 (AQP4).

Ultomiris contains the active substance ravulizumab.

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How is Ultomiris used?

The medicine can only be obtained with a prescription and must be given under the guidance and supervision of a doctor who has experience in the management of patients with kidney disorders and disorders affecting the nervous system or the blood.

Ultomiris is given as an infusion (drip) into a vein; for PHN and aHUS, Ultomiris can also be given as an injection under the skin.

For PNH, gMG and NMOSD, this is a life-long treatment. For aHUS, the medicine is given for at least 6 months, but the doctor will consider the length of treatment for each patient individually. Patients are monitored for any reactions during the infusion and for at least one hour afterwards. In case of any infusion-related reactions, the doctor may slow down or stop the infusion.

For more information about using Ultomiris, see the package leaflet or contact your doctor or pharmacist.

How does Ultomiris work?

The active substance in Ultomiris, ravulizumab, is a monoclonal antibody (a type of protein) designed to attach to the C5 complement protein, which is a part of the immune system called the "complement system".

In PNH, aHUS, gMG and NMOSD, the complement proteins are over-active, causing the destruction of red blood cells in PNH, the formation of blood clots in small blood vessels throughout the body (thrombotic microangiopathy) in aHUS, the damage to receptors at the junction between nerves and muscles resulting in muscular weakness in gMG, and the damage to nerve cells seen in patients with NMOSD. By blocking the C5 complement protein, Ultomiris prevents the immune system from damaging cells, thereby helping to control symptoms of these diseases.

What benefits of Ultomiris have been shown in studies?

Paroxysmal nocturnal haemoglobinuria

Ultomiris was shown in 2 studies in adults to be as effective as eculizumab in reducing the breakdown of red blood cells and avoiding the need for transfusions in patients with PNH.

In the first study, 246 patients with PNH who previously had not been treated with a complement inhibitor, such as eculizumab, received either Ultomiris or eculizumab. After 6 months of treatment, similar benefits were seen in both groups, with two-thirds or more of patients (74% given Ultomiris and 66% given eculizumab) not needing red blood cell transfusions. In addition, around half of the patients in both groups had achieved normal blood levels of the enzyme LDH.

In the second study in 195 patients with PNH who did not have symptoms after at least 6 months of treatment with eculizumab, patients either continued treatment with eculizumab or switched to Ultomiris. The change in blood levels of LDH after 6 months of treatment was similar in the 2 groups. In addition, none of the patients treated with Ultomiris had a flare-up of symptoms during this time, in comparison to 5 of those continuing with eculizumab.

A third ongoing study showed comparable benefits from Ultomiris in 13 patients aged between 9 and 17 years who had either not been treated previously with a complement inhibitor or were stable on treatment with eculizumab. After 6 months of treatment, 3 of 5 previously untreated patients and 4 of 8 eculizumab-experienced patients had normal levels of LDH. In addition, 3 of the 5 previously untreated and all 8 of the previously treated patients did not need blood transfusions during treatment.

The company also provided supportive data to show that the way the medicine acts and is distributed in the body is similar in children and adults.

An additional study in 128 patients with PNH showed that Ultomiris given by injection under the skin is as effective as when the medicine is given by infusion.

Atypical haemolytic uremic syndrome

Ultomiris was effective at reducing symptoms of aHUS in 2 main studies. The studies looked at the number of patients who achieved a 'complete thrombotic microangiopathy (TMA) response', meaning patients with platelet and LDH levels within normal range and a minimum 25% improvement in serum creatinine (a marker of kidney function), over 6 months of treatment.

In the first study, 30 out of 56 adults and adolescents (54%) with aHUS who had not been treated with a complement inhibitor before achieved a complete TMA response. The second study involved children and adolescents who had either not been treated with a complement inhibitor before or who had received eculizumab. In this study 14 out of 18 patients (78%) had a complete TMA Response. There were not enough data in children under 2 years of age to demonstrate the effectiveness of Ultomiris in children weighing less than 10 kg.

Generalised myasthenia gravis

Ultomiris was compared with placebo (a dummy treatment) in one main study involving 175 adult patients, who had symptoms despite receiving standard treatment for their disease. Treatment with Ultomiris improved patients' symptoms and their ability to undertake daily activities based on a standard scoring system called MG-ADL, which measures the impact of the disease on the patients' daily activities. The scale ranges from 0 to 24 and higher scores indicate more severe symptoms. After 26 weeks, Ultomiris led to a 3.1 point reduction in the MG-ADL score, whereas placebo led to a 1.4 point reduction.

Neuromyelitis optica spectrum disorders

One (ongoing) study involving 58 adults with NMOSD who had AQP4 antibodies showed that Ultomiris was effective at increasing the length of time between relapses (flare-ups of NMOSD symptoms). During the first phase of the study, which lasted between 50 weeks and 2,5 years (depending on when a patient first entered the study), there were no flare-ups of symptoms in patients given Ultomiris.

What are the risks associated with Ultomiris?

For the full list of side effects and restrictions with Ultomiris, see the package leaflet.

The most common side effects with Ultomiris (which may affect more than 1 in 10 people) are diarrhoea, nasopharyngitis (inflammation of the nose and throat), upper respiratory tract infections (infections of the nose and throat) and headache. The most serious side effect is meningococcal infection, a bacterial infection caused by *Neisseria meningitidis* that can cause meningitis and blood poisoning.

Patients treated with Ultomiris are more prone to infections, including severe meningococcal disease, therefore, Ultomiris must not be used in patients who have an ongoing meningococcal infection. It must not be used in patients who have not been vaccinated against this infection unless they are taking appropriate antibiotics to reduce the risk of infection. Patients must take antibiotics for 2 weeks after they have been vaccinated.

Why is Ultomiris authorised in the EU?

Ultomiris is as effective as eculizumab in treating patients with PNH, reducing the breakdown of red blood cells and avoiding the need for transfusions. Although data was not available from patients weighing less than 30 kg, benefits were expected to be similar in these patients; dosage in those weighing at least 10 kg could be based on that in aHUS and further evidence from other studies.

In aHUS, Ultomiris was not compared with eculizumab, however the European Medicines Agency concluded based on the data provided that the benefits in adults and children weighing at least 10 kg were clinically significant. The Agency also noted that Ultomiris has a more convenient treatment schedule than eculizumab (with one infusion every 8 weeks instead of every 2 weeks). As for its safety, Ultomiris has similar side effects to eculizumab.

In gMG, Ultomiris was more effective than placebo at controlling symptoms of the disease, based on the results of studies which measured both the patients' and physicians' assessment of treatment on the impact of the disease in terms of ability to undertake daily activities. The Agency also concluded that patients treated with Ultomiris were less likely to experience either worsening of their disease and require hospitalisation or treatment with rescue medicines, compared to those treated with placebo. With regards to safety, no new side effects were identified when Ultomiris was used to treat patients with gMG.

In NMOSD, Ultomiris was shown to be effective at increasing the length of time between relapses; side effects were similar to those observed for the medicine's other uses.

The Agency therefore decided that Ultomiris' benefits are greater than its risks and it can be authorised for use in the EU.

What measures are being taken to ensure the safe and effective use of Ultomiris?

The company that markets Ultomiris will ensure that the medicine is only made available to patients when healthcare professionals have made a written declaration that they have been vaccinated or are receiving antibiotic treatment to prevent meningococcal disease. The company will also provide prescribers and patients with information on the safety of the medicine, and will send reminders to prescribers and pharmacists to check if re-vaccination is needed for patients taking Ultomiris. Patients will also be given a special card that explains the symptoms of meningococcal infection, instructing patients to seek medical care immediately if they experience them.

Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Ultomiris have also been included in the summary of product characteristics and the package leaflet.

As for all medicines, data on the use of Ultomiris are continuously monitored. Side effects reported with Ultomiris are carefully evaluated and any necessary action taken to protect patients.

Other information about Ultomiris

Ultomiris received a marketing authorisation valid throughout the EU on 2 July 2019.

Further information on Ultomiris can be found on the Agency's website: ema.europa.eu/medicines/human/EPAR/ultomiris.

This overview was last updated in 06-2023.