Package leaflet: Information for the user

Ultomiris 1,100 mg/11 mL concentrate for solution for infusion
ravulizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ultomiris is and what it is used for

What is Ultomiris
Ultomiris is a medicine that contains the active substance ravulizumab and it belongs to a class of medicines called monoclonal antibodies, that attach to a specific target in the body. Ravulizumab has been designed to attach to the C5 complement protein, which is a part of the body's defence system called the 'complement system'.

What is Ultomiris used for
Ultomiris is used to treat adult and children patients 10 kg and over with a disease called paroxysmal nocturnal haemoglobinuria (PNH), including patients untreated with complement inhibitor and patients who have received eculizumab for at least the past 6 months. In patients with PNH, the complement system is overactive and attacks their red blood cells, which can lead to low blood counts (anaemia), tiredness, difficulty in functioning, pain, abdominal pain, dark urine, shortness of breath, difficulty swallowing, erectile dysfunction and blood clots. By attaching to and blocking the C5 complement protein, this medicine can stop complement proteins from attacking red blood cells and so control symptoms of the disease.

Ultomiris is also used to treat patients 10 kg and over with a disease affecting the blood system and kidney called atypical haemolytic uremic syndrome (aHUS), including patients untreated with complement inhibitor and patients who have received eculizumab for at least 3 months. In patients with aHUS, their kidneys and blood vessels, including platelets, can be inflamed which can lead to low blood counts (thrombocytopenia and anaemia), reduced or lost kidney function, blood clots, tiredness and difficulty in functioning. Ultomiris can block the body's inflammatory response, and its ability to attack and destroy its own vulnerable blood vessels and so control symptoms of the disease including injury to the kidneys.

2. What you need to know before you use Ultomiris

Do not use Ultomiris:
- If you are allergic to ravulizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have not been vaccinated against meningococcal infection.
- If you have meningococcal infection.

Warnings and precautions
Talk to your doctor before using Ultomiris.

Meningococcal and other *Neisseria* infections symptoms
Because the medicine blocks the complement system, which is part of the body's defences against infection, the use of Ultomiris increases your risk of meningococcal infection caused by *Neisseria meningitidis*. These are severe infections affecting the linings of the brain and can spread throughout the blood and body (sepsis).

Consult your doctor before you start Ultomiris to be sure that you receive vaccination against *Neisseria meningitidis* at least 2 weeks before beginning therapy. If you cannot be vaccinated 2 weeks beforehand, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated. Ensure that your current meningococcal vaccination is up to date. You should also be aware that vaccination may not always prevent this type of infection. In accordance with national recommendations, your doctor might consider that you need supplementary measures to prevent infection.

Meningococcal infection symptoms

Because of the importance of rapidly identifying and treating meningococcal infection in patients who receive Ultomiris, you will be provided a 'Patient card' to carry with you at all times, listing relevant signs and symptoms of meningococcal infection/sepsis.
If you experience any of the following symptoms, you should immediately inform your doctor:
- headache with nausea or vomiting
- headache and fever
- headache with a stiff neck or stiff back
- fever
- fever and rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Treatment for meningococcal infection while travelling

If you are travelling in a region where you are unable to contact your doctor or will be temporarily unable to receive medical treatment, your doctor may prescribe an antibiotic against *Neisseria meningitidis* to bring with you. If you experience any of the symptoms described above, you should take the course of antibiotics as prescribed. You should bear in mind that you should still see a doctor as soon as possible, even if you feel better after having taken the antibiotics.

Infections
Before starting Ultomiris, inform your doctor if you have any infections.

Infusion reactions
When Ultomiris is given, you may experience reactions to the infusion (drip) (infusion reaction) such as headache, lower back pain, and infusion-related pain. Some patients may experience allergic or hypersensitivity reactions (including anaphylaxis, a serious allergic reaction which causes difficulty breathing or dizziness).

Children and adolescents
Patients less than 18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections.

Other medicines and Ultomiris
Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines.

Pregnancy, breast-feeding, and fertility

Women of childbearing potential

The effects of the medicine on an unborn child are not known. Therefore, effective contraception during treatment and up to 8 months after treatment should be used in women who are able to get pregnant.

Pregnancy/ Breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.
Ultomiris is not recommended during pregnancy and in women of childbearing potential not using contraception.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines.

Ultomiris contains sodium
Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, this medicine contains 0.18 g sodium (main component of cooking/table salt) in 72 mL at the maximal dose. This is equivalent to 9.1% of the recommended maximum daily dietary intake of sodium for an adult. You should take this into consideration if you are on a controlled sodium diet.

3. How to use Ultomiris

At least 2 weeks before you start treatment with Ultomiris, your doctor will give you a vaccine against meningococcal infections if you have not previously had one or if your vaccination is outdated. If you cannot be vaccinated at least 2 weeks before you start treatment with Ultomiris, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated.
If your child is less than 18 years, your doctor will administer a vaccine (if not yet done) against *Haemophilus influenzae* and pneumococcal infections according to the national vaccination recommendations for each age group.

Instructions for proper use
Your dose of Ultomiris will be calculated by your doctor, based on your body weight, as shown in Table 1. Your first dose is called the loading dose. Two weeks after receiving your loading dose, you will be given a maintenance dose of Ultomiris, and this will then be repeated once every 8 weeks for patient above 20 kg and every 4 weeks for patient less than 20 kg.

If you were previously receiving another medicine for PNH and aHUS called eculizumab, the loading dose should be given 2 weeks after the last eculizumab infusion.

Table 1: Ultomiris weight-based dosing regimen

Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)
10 to less than 20	600	600
20 to less than 30	900	2,100
30 to less than 40	1,200	2,700
40 to less than 60	2,400	3,000
60 to less than 100	2,700	3,300
above 100	3,000	3,600

Ultomiris is given by infusion (drip) into a vein. The infusion will take approximately 45 min.

If you receive more Ultomiris than you should
If you suspect that you have been accidentally given a higher dose of Ultomiris than prescribed, please contact your doctor for advice.

If you forget an appointment to receive Ultomiris
If you forget an appointment, please contact your doctor immediately for advice and see section below "If you stop using Ultomiris".

If you stop using Ultomiris for PNH
Interrupting or ending treatment with Ultomiris may cause your PNH symptoms to return with greater severity. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely for at least 16 weeks.

The risks of stopping Ultomiris include an increase in the destruction of your red blood cells, which may cause:
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- A significant fall in your red blood cell counts (anaemia),
- Dark urine,
- Fatigue,
- Abdominal pain,
- Shortness of breath,
- Difficulty swallowing,
- Erectile dysfunction (impotence),
- Confusion or change in how alert you are,
- Chest pain, or angina,
- An increase in your serum creatinine level (problems with your kidneys), or
- Thrombosis (blood clotting).

If you have any of these symptoms, contact your doctor.

If you stop using Ultomiris for aHUS
Interrupting or ending treatment with Ultomiris may cause your aHUS symptoms to come back. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely.

The risks of stopping Ultomiris include an increase in small blood vessel damage, which may cause:
- A significant fall in your platelets (thrombocytopenia),
- A significant rise in destruction of your red blood cells,
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- Decreased urination (problems with your kidneys),
- An increase in your serum creatinine level (problems with your kidneys),
- Confusion or change in how alert you are,
- Change in your vision

- Chest pain, or angina,
- Shortness of breath,
- Abdominal pain, diarrhoea, or
- Thrombosis (blood clotting).

If you have any of these symptoms, contact your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Your doctor will discuss the possible side effects with you and explain the risks and benefits of Ultomiris with you prior to treatment.

The most serious side effect is meningococcal infection/sepsis.
If you experience any of the meningococcal infection symptoms (see section 2 Meningococcal infection symptoms), you should immediately inform your doctor.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

Very common (may affect more than 1 in 10 people):
- Headache
- Nausea, diarrhoea,
- Upper respiratory tract infection
- Common cold (nasopharyngitis)
- Fever (pyrexia), feeling tired (fatigue)

Common (may affect up to 1 in 10 people):
- Dizziness
- Abdominal pain, vomiting, stomach discomfort after meals (dyspepsia)
- Rash, itchy skin (pruritus)
- Back pain, joint pain (arthralgia), muscle pain (myalgia) and muscle spasms
- Influenza like illness, feeling tired (asthenia)
- Infusion related reaction

Uncommon (may affect up to 1 in 100 people):
- Meningococcal infection
- Chills
- Serious allergic reaction which causes difficulty in breathing or dizziness (anaphylactic reaction), hypersensitivity

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed below.
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to Alexion Pharma UK Ltd on uk.adverseevents@alexion.com, Freephone (UK): 0800321 3902.
By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ultomiris

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.
Store in a refrigerator (2 °C–8 °C).
Do not freeze.

Store in the original package in order to protect from light.
After dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection, the medicine should be used immediately, or within 24 hours if refrigerated or within 4 hours at room temperature.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ultomiris contains

- The active substance is ravulizumab. Each vial of solution contains 1,100 mg of ravulizumab.
- The other ingredients are: sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, polysorbate 80, arginine, sucrose, water for injections

This medicine contains sodium (see section 2 "Ultomiris contains sodium").

What Ultomiris looks like and contents of the pack
Ultomiris is presented as a concentrate for solution for infusion (11 mL in a vial – pack size of 1).
Ultomiris is a translucent, clear to yellowish colour, practically free from particles solution.

Marketing Authorisation Holder
Alexion Europe SAS
103-105, rue Anatole France
92300 Levallois-Perret
France

Manufacturer
Alexion Pharma International Operations Unlimited Company
Alexion Dublin Manufacturing Facility
College Business and Technology Park
Blanchardstown Rd North
Dublin 15 R925
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Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
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The following information is intended for healthcare professionals only:

Instructions for Use for Healthcare Professionals
Handling Ultomiris

1- How is Ultomiris supplied?

Each vial of Ultomiris contains 1,100 mg of active substance in 11 mL of product solution.

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

2- Before administration

Dilution should be performed in accordance with good practices rules, particularly for the respect of asepsis.

In the absence of compatibility studies, Ultomiris 1,100 mg/11 mL concentrate for solution for infusion must not be mixed with Ultomiris 300 mg/30 mL concentrate for solution for infusion.

Ultomiris should be prepared for administration by a qualified healthcare professional using aseptic technique.

- Visually inspect Ultomiris solution for particulate matter and discolouration.
- Withdraw the required amount of Ultomiris from the vial(s) using a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute Ultomiris to a final concentration of 50 mg/mL (initial concentration divided by 2) by adding the appropriate amount of sodium chloride 9 mg/mL (0.9%) solution for injection to the infusion as per the instructions provided in table below.

Table 1: Loading dose administration reference table

Body weight range (kg)[a]	Loading dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)	Minimum infusion duration minutes (hours)
≥ 10 to < 20	600	6	6	12	45 (0.8)
≥ 20 to < 30	900	9	9	18	35 (0.6)
≥ 30 to < 40	1,200	12	12	24	31 (0.5)
≥ 40 to < 60	2,400	24	24	48	45 (0.8)
≥ 60 to < 100	2,700	27	27	54	35 (0.6)
≥ 100	3,000	30	30	60	25 (0.4)

[a] Body weight at time of treatment

[b] Ultomiris should only be diluted using sodium chloride 9 mg/mL (0.9 %) solution for injection

Table 2: Maintenance dose administration reference table

Body weight range (kg)[a]	Maintenance dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)	Minimum infusion duration minutes (hours)
≥ 10 to < 20	600	6	6	12	45 (0.8)
≥ 20 to < 30	2,100	21	21	42	75 (1.3)
≥ 30 to < 40	2,700	27	27	54	65 (1.1)
≥ 40 to < 60	3,000	30	30	60	55 (0.9)
≥ 60 to < 100	3,300	33	33	66	40 (0.7)
≥ 100	3,600	36	36	72	30 (0.5)

[a] Body weight at time of treatment

[b] Ultomiris should be only diluted using sodium chloride 9 mg/mL (0.9 %) solution for injection

- Gently agitate the infusion bag containing the diluted Ultomiris solution to ensure thorough mixing of the medicinal product and diluent. Ultomiris should not be shaken.
- The diluted solution should be allowed to warm to room temperature (18 °C–25 °C) prior to administration by exposure to ambient air during approximately 30 min.
- The diluted solution must not be heated in a microwave or with any heat source other than the prevailing room temperature.
- Discard any unused portion left in a vial as the medicinal product contains no preservatives.
- The prepared solution should be administered immediately following preparation. Infusion must be administered through a 0.2 µm filter.
- If the medicinal product is not used immediately after dilution, storage times must not exceed 24 hours at 2 °C–8 °C or 4 hours at room temperature taking into account the expected infusion time.

3- Administration

- Do not administer Ultomiris as an intravenous push or bolus injection.
- Ultomiris should only be administered via intravenous infusion.
- The diluted solution of Ultomiris should be administered by intravenous infusion over approximately 45 min using a syringe-type pump or an infusion pump. It is not necessary to protect the diluted solution of Ultomiris from light during administration to the patient.

The patient should be monitored for one hour following infusion. If an adverse event occurs during the administration of Ultomiris, the infusion may be slowed or stopped at the discretion of the physician.

4- Special handling and storage

Store in a refrigerator (2 °C–8 °C). Do not freeze. Store in the original package in order to protect from light.

Do not use this medicine after the expiry date which is stated on the carton after ‘EXP’. The expiry date refers to the last day of that month.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.