HOW LONG WILL I NEED TO TAKE ULTOMIRIS®?

Since **PNH is a chronic disease**, ULTOMIRIS is intended to be an **ongoing therapy**. Patients who start ULTOMIRIS® should continue receiving ULTOMIRIS®, even if they feel better.

Interrupting or ending treatment with ULTOMIRIS® may cause your PNH symptoms to come back more severely soon after stopping ULTOMIRIS® treatment.

YOU MUST NOT STOP THE TREATMENT WITHOUT MEDICAL SUPERVISION

If you plan to stop treatment with ULTOMIRIS®, you need to discuss beforehand with your doctor the possible side effects and risks, which include an increase in the destruction of your red blood cells (haemolysis) that may cause:

- A significant fall in red blood cell count (anemia)
- You to become confused or less alert
- Chest pain or angina
- Problems with the kidneys (increase in serum creatinine level)
- Blood clotting (thrombosis)

REFERENCES

1. ULTOMIRIS® Israeli approved PIL.
2. Hillmen P, Young NS, Shubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2006;355:1233-1243.
3. Rosse WF, Hillmen P, Schreiber AD. Immune-mediated hemolytic anemia. *Hematology (Am Soc Hematol Educ Program)*. January 2004:48-62.

In case of safety concerns, please call:
1-800-250-255

ALEXION™

Patient Information Brochure

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ALEXION

Glossary of Terms

Anaemia
A condition in which your body does not have enough red blood cells; this may lead to fatigue and other symptoms.

Anticoagulants
Sometimes referred to as blood thinners, anticoagulants are drugs that decrease the clotting ability of blood and help prevent the formation of blood clots.

Blood clots
When many platelets in the blood stick together, they form a blood clot. These clots can block blood flow in the veins and arteries, depending on their size and location (see “Thrombosis”).

Chronic haemolysis
The destruction of red blood cells (haemolysis) over a long period of time (chronic).

Complement system (also known as the complement cascade or just complement)
Part of your immune system that destroys bacteria and other foreign cells. In PNH, complement is responsible for the destruction of red blood cells that lack specific protective proteins.

Gonococcal infection
Infection sexually transmitted and caused by the bacterium Neisseria gonorrhoeae (also named gonorrhea). Can disseminate and cause widespread blood infection (sepsis).

Haemoglobin
The brownish-red substance in red blood cells that carries oxygen throughout your body. Responsible for the characteristic dark urine seen in PNH.

Haemoglobinuria
Haemoglobin in the urine. This is the technical term for the dark “cola-coloured” urine which is sometimes seen in PNH. When the red blood cells are lysed or destroyed, as they are in PNH, haemoglobin is released from the red blood cells. When it is not all processed by the body’s system, it is sent out as waste and colours the urine a characteristic cola- brown colour.

Meningococcal infection
Infection caused by the bacterium Neisseria meningitidis (also named meningococcus). Can cause meningitis or widespread blood infection (sepsis).

Sepsis
The presence of bacteria (bacteremia), other infectious organisms, or toxins created by infectious organisms in the bloodstream that spread throughout the body.

Paroxysmal Nocturnal Haemoglobinuria (PNH)
A rare blood disorder in which red blood cells are chronically destroyed or haemolysed by the complement system. This can lead to severe problems including anaemia, fatigue and thrombosis.

Red blood cells
Blood cells that carry oxygen using a protein complex called haemoglobin. PNH red blood cells are continually attacked and destroyed by the complement system because they are missing important protectiveproteins.

Thrombosis (thrombotic events)
The formation or development of a blood clot that often blocks blood from flowing through a vessel. In PNH, blood clots can occur in common places, but can also occur in unusual sites, such as in vessels in the abdomen (see Blood clots).

Introduction

This guide is for adult patients suffering from Paroxysmal Nocturnal Haemoglobinuria (PNH). The guide gives you information about ULTOMIRIS®, how it will be given to you and about important safety information that you must be aware of.

What is ULTOMIRIS®?

ULTOMIRIS® is a medication that is used to treat adult patients with PNH. It is a type of humanised monoclonal antibody. Antibodies are substances which in the blood can bind to specific targets. Humanised describes the fact that the antibody has been engineered to make it as similar to human antibodies as possible. Monoclonal means that all of the medication comes from one original antibody, i.e., they are all exactly the same.

PNH is a disease where a specific part of the natural immune system, called the complement system, is overactive, usually due to a genetic defect in the normal regulation of the complement system. The complement system is always switched on and when it is overactive it can destroy red blood cells (haemolysis) which can lead to low blood counts (anaemia), tiredness, difficulty in functioning, pain, dark urine, shortness of breath and blood clots.

ULTOMIRIS® is an antibody which binds to one of the parts of the complement system and makes it inactive. Therefore, ULTOMIRIS® reduces the haemolysis (destruction of red blood cells) which is the cause of the signs and symptoms of PNH. As PNH is a chronic disease, ULTOMIRIS® is intended as long-term treatment.

HAEMOLYSIS OF RED BLOOD CELLS

HEALTHY RED BLOOD CELLS

FAQs

WHAT ARE THE SAFETY CONSIDERATIONS RELATED TO ULTOMIRIS®?

Important Safety Information

As ULTOMIRIS® blocks a part of your immune system it increases the risk of severe infection and sepsis, especially by a type of bacteria called *Neisseria meningitidis*. This can cause cases of meningitis which is a major brain inflammation or a severe infection of the blood.

These infections require urgent and appropriate care as it may become rapidly fatal or life-threatening or lead to major disabilities.

It is important to understand the precautions to take to reduce the risk of these infections and what to do if you are worried you may have an infection (see below).

As a safety precaution:

YOU MUST BE VACCINATED against meningococcal infection before starting ULTOMIRIS®. If you initiate ULTOMIRIS® treatment less than 2 weeks after receiving a meningococcal vaccine you must receive antibiotic (s) until 2 weeks after vaccination to reduce the risk of infection with *Neisseria meningitidis*.

Vaccination reduces the risk of developing meningococcal infection, but it does not eliminate the risk completely.

If the vaccine is contraindicated to you or not available in your country, you will be given antibiotic(s) throughout the treatment period.

YOU MUST CARRY YOUR SAFETY CARD AT ALL TIMES WHILE ON ULTOMIRIS® AND FOR 8 MONTHS AFTER YOU STOP TAKING IT and present it to any healthcare providers you may see.

WHAT ARE THE SYMPTOMS THAT SHOULD ALERT ME DURING TREATMENT?

YOU WILL NEED TO BE AWARE OF THE SIGNS AND SYMPTOMS OF MENINGOCOCCAL INFECTION AND NOTIFY YOUR DOCTOR IMMEDIATELY IF ANY OF THE FOLLOWING SYMPTOMS OCCUR:

- Headache with nausea or vomiting
- Headache and a fever
- Headache with a stiff neck or stiff back
- Fever
- Fever and a rash
- Confusion
- Muscle aches with flu-like symptoms
- Eyes sensitive to light

IF YOU CANNOT REACH YOUR DOCTOR, GO TO AN EMERGENCY DEPARTMENT.
SHOW THEM YOUR PATIENT SAFETY CARD.

ARE THERE STEPS I SHOULD TAKE BEFORE STARTING THERAPY?

Prior to commencing treatment, your doctor will discuss with you the importance of:

- Receiving vaccines against meningitis and in some cases specific antibiotic(s) to reduce the risk of infection with a type of bacteria called *Neisseria meningitidis*
- Understanding the symptoms associated with infections listed in your safety card and what to do if you experience those symptoms
- Being carefully monitored by your doctor following any discontinuation of ULTOMIRIS® treatment

Your doctor or nurse will make sure you receive a vaccine against meningococcal infection at least 2 weeks before the first infusion. If you initiate ULTOMIRIS® treatment less than 2 weeks after receiving meningococcal vaccine your doctor or nurse will make sure you receive antibiotic(s) until 2 weeks after vaccination to reduce the risk of infection with *Neisseria meningitidis*.

In addition, you will be closely monitored for meningococcal and other infections during the course of your treatment.

ARE THERE OTHER CONSIDERATIONS WHILE I AM ON ULTOMIRIS®?

Risk of Serious Infections: Due to its mechanism of action, ULTOMIRIS® should be administered with caution to patients with active systemic infections. You should monitor your symptoms and report any changes to your doctor. You may also be at risk of other infections with bacteria called Neisseria including disseminated gonococcal infection. If you are at risk of gonorrhoea, ask your doctor or pharmacist for advice before using this medicine. There is also a potential risk of non-neisserial infections during ravulizumab therapy.

Haematological Abnormalities and Malignancies: As a PNH patient, you will be monitored for haematological changes. The PNH laboratory monitoring may potentially alert your physician to haematological abnormalities and malignancies. The PNH laboratory monitoring continues during ravulizumab treatment and for a period not less than 16 weeks after ravulizumab discontinuation.

Immune Reactions and Drug Hypersensitivity: ULTOMIRIS® contains a protein and proteins can cause allergic reactions in some people. If you experience any signs or symptoms after receiving ULTOMIRIS®, you should consult your healthcare professional.

Pregnancy: ULTOMIRIS® is not recommended during pregnancy. Tell your doctor before starting treatment with ULTOMIRIS® if you are pregnant or plan to become pregnant. Women of childbearing potential should use adequate contraception methods during treatment and up to 8 months after treatment.

Male patients on ULTOMIRIS® should not father a child or donate sperm up to 8 months after treatment.

Breast-feeding: ULTOMIRIS® may pass through your breast milk to your baby. Therefore, you should not breast-feed during ULTOMIRIS® treatment and up to 8 months after treatment.

Elderly: There are no special precautions for treated patients aged 65 years and older.

Undesirable Effects: ULTOMIRIS® is generally well-tolerated. The most commonly reported side effect was upper respiratory tract infection, common cold, and headache and the most serious side effect was meningococcal infection (i.e. infection by Neisseirra meningitidis). Most headaches were mild and did not persist after the initial administration phase of ULTOMIRIS®.

HOW DO I GET STARTED ON ULTOMIRIS® THERAPY?

ULTOMIRIS® must be prescribed by a doctor.

You will also be given a starter's kit containing:

- **Patient Safety Card:** it is very important to rapidly identify and treat certain types of infection in patients who receive ULTOMIRIS®; therefore, you will be given a Safety Card which lists specific symptoms for which you should always look for. You should carry this card at all times while on ULTOMIRIS® and for 8 months after last dose and show it to any healthcare professional you see.
- **Patient Information Brochure**

Your doctor will also ask you if you would like to participate in the **PNH Registry** and will register you if you agree.

HOW IS ULTOMIRIS® ADMINISTERED?

ULTOMIRIS® is administered through an **intravenous infusion** (introduction of a solution into a vein). The infusion time varies based on dosage. It must be prepared and administered by a doctor or other suitably qualified healthcare professional.

As with all drugs administered through an intravenous infusion, ULTOMIRIS® may cause immediate or delayed reaction. Please refer to your doctor if that happens.

Because there is a risk of infusion reaction (including allergic reaction), following each infusion you will be monitored for about one hour. Your doctor's instructions should be carefully observed.

WHAT DOSE OF ULTOMIRIS® IS USED?

For adults:

The recommended dosing regimen for adult patients with PNH consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. The doses to be administered are based on the patient's body weight, as shown in *Table 1*, and for minimum infusion times as shown in *Table 2*.

Maintenance doses are administered once every 8 weeks, starting 2 weeks after loading dose administration

Table 1: Weight-based Dosing

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg)
≥ 40 to < 60	2400	3000
≥ 60 to < 100	2700	3300
≥ 100	3000	3600

Table 2: Dose Administration Reference Table

	Body Weight Range (kg)	Ultomiris® Dose (mg)	Total Volume (mL)	Minimum Infusion Duration (Minutes (hours))
Loading Dose	≥ 40 to < 60	2400	480	114 (1.9)
	≥ 60 to < 100	2700	540	102 (1.7)
	≥ 100	3000	600	108 (1.8)
Maintenance Dose	≥ 40 to < 60	3000	600	140 (2.4)
	≥ 60 to < 100	3300	660	120 (2.0)
	≥ 100	3600	720	132 (2.2)

It is very important to make sure that you **do not miss or postpone any scheduled treatment appointment** in order to continue to control haemolysis and experience the full benefits of ULTOMIRIS® therapy.

Reporting of side effects

Side effects can be reported to the Israeli Ministry of Health by clicking on the link “Report Side Effects of Drug Treatment” that appears on the homepage of the Ministry of Health’s website (www.health.gov.il) which links to a portal, or by the following link: https://sideeffects.health.gov.il/ and by emailing the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com
Tel: 1-800-250-255

For further information, please refer to the Israeli approved patient leaflet.