REFERENCES

1. ULTOMIRIS® (ravulizumab) Israeli approved SmPC.

2. Rosse WF, Hillmen P, Schreiber AD. Immune-mediated hemolytic anemia. *Hematology* (*Am Soc Hematol Educ Program*). 2004:48-62.

For more information about ULTOMIRIS® email:
drugsafety@neopharmgroup.com

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

Please refer to the Israeli approved SmPC for ULTOMIRIS, including information regarding serious meningococcal infection.

ALEXION™

PHYSICIAN'S GUIDE TO PRESCRIBING for patients with PNH

ALEXION

This document was last approved in February 2020 by The Israeli Ministry of Health (MOH)

What is ULTOMIRIS®

ULTOMIRIS® is a recombinant humanised monoclonal antibody targeting the complement protein C5. It protects PNH red blood cells from chronic intravascular haemolysis by specifically binding to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and preventing the generation of the terminal complement complex C5b-9. Therefore, ULTOMIRIS® inhibits terminal complement mediated intravascular haemolysis in PNH patients.[1]

HAEMOLYSIS OF RED BLOOD CELLS

HEALTHY RED BLOOD CELLS

ULTOMIRIS® Indications[1]

ULTOMIRIS® is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):

- in patients with haemolysis with clinical symptom(s) indicative of high disease activity
- in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months

Please refer to the Israeli approved SmPC for ULTOMIRIS, including information regarding serious meningococcal infection

ULTOMIRIS® Safety Profile[1]

IMPORTANT SAFETY INFORMATION[1]

Due to its mechanism of action, the use of ULTOMIRIS® increases the risk of meningococcal infection (*Neisseria meningitidis*) for the patient.

The following steps must be taken to minimise the risk of meningococcal infection and the risk of poor outcomes following infection:

- **Provide your patients with meningococcal vaccinations and/or prophylactic antibiotics as explained below:**
  - **Vaccinate your patients with a meningococcal vaccine at least 2 weeks** prior to initiating ULTOMIRIS® unless the risk of delaying ULTOMIRIS® therapy outweighs the risk of developing a meningococcal infection
  - **Vaccines against serogroups A, C, Y, W135 and B** (where available) are recommended.
  - **Vaccination or revaccination** may further activate complement and, as a result, patients with complement-mediated diseases, including PNH, **may experience increased signs and symptoms of their underlying disease, such as haemolysis** (PNH).
  - **Revaccinate** according to current national vaccination guidelines for vaccine use.
  - In patients for whom the vaccine is **contra-indicated** and in patients treated **with ULTOMIRIS® less than 2 weeks** after receiving a meningococcal vaccine, **treat with antibiotic prophylaxis** throughout the treatment period or until 2 weeks after the vaccination can be given.

- **Monitor** your patients for early signs of meningococcal infections, evaluate immediately if infection is suspected, and treat with antibiotics if necessary.

- **Provide a Patient Information Brochure** (to patients). **Explain the brochure** to patients being treated with **ULTOMIRIS®** in order to increase their awareness of potential meningococcal infections and the relevant signs and symptoms which include:

- 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

- **Provide a Patient Safety Card** to patients being treated with **ULTOMIRIS®** and explain that they must carry it at all times while on **ULTOMIRIS®** and for 8 months after last dose and show it to healthcare professionals they see.

- **Inform patients that if they suspect they may have an infection, they should seek urgent medical advice.**

Other Systemic Infections: ULTOMIRIS® therapy should be administered with caution to patients with active systemic infections.
Serious infections with Neisseria species (other than Neisseria meningitidis), including disseminated gonococcal infections, have been reported with other terminal complement inhibitors.
Physicians should advise patients about gonorrhoea prevention.

Please refer to the Israeli approved SmPC for ULTOMIRIS, including information regarding serious meningococcal infection

IMPORTANT SAFETY INFORMATION[1] *(cont.)*

Contraindications:

- Hypersensitivity to the active substance or to any of the excipients in ULTOMIRIS®
- Patients with unresolved *Neisseria meningitidis* infection at treatment initiation
- Patients who are not currently vaccinated against *Neisseria meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination

Paediatric Population: The safety profile in paediatric patients with PNH treated with ULTOMIRIS® has not yet been established. ULTOMIRIS® should not be used in children and adolescents.

Geriatric Patients: ULTOMIRIS® may be administered to patients with PNH aged 65 years and over. There is no evidence indicating any special precautions are required for treating a geriatric population.

Renal Impairment: The safety and efficacy of ULTOMIRIS® has not been studied in patients with renal impairment.

Hepatic Impairment: The safety and efficacy of ULTOMIRIS® has not been studied in patients with hepatic impairment.

Fertility, Pregnancy and Lactation: For ULTOMIRIS®, no clinical data on exposed pregnancies is available. ULTOMIRIS® should be given to a pregnant woman only if clearly needed. Women of childbearing potential must use effective contraception during treatment and up to 8 months after treatment.

Breast-feeding should be discontinued 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.

Infusion Reactions: As with all therapeutic proteins, administration of ULTOMIRIS® may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis).

Physicians are reminded to monitor patients for signs of immune reactions during ULTOMIRIS® infusion and to consider proportionate supportive measures for patients experiencing infusion reactions.

In clinical trials, no patients with PNH experienced an infusion reaction requiring discontinuation of ULTOMIRIS®.

Haematological Abnormalities and Malignancies: Physicians are reminded that PNH patients should be monitored for haematological changes. This includes PNH patients treated with ravulizumab, where PNH laboratory monitoring should potentially alert physicians to haematological abnormalities and malignancies during ravulizumab treatment, and for a period not less than 16 weeks after ravulizumab discontinuation.

Risk of haemolysis: After ULTOMIRIS® discontinuation in PNH patients there may be a risk of serious haemolysis. See notes on Treatment Discontinuation.

Immunogenicity: Treatment with any therapeutic protein may induce an immune response. In PNH patient studies (N = 261), only 1 (0.38%) case of development of treatment-emergent anti-drug antibody has been reported with Ultomiris. There has been no observed correlation of antibody development to clinical response or adverse events.

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STARTING YOUR PATIENT ON ULTOMIRIS®[1]

To successfully start your patient on ULTOMIRIS®, there are some steps you need to take:

- **Vaccinate** your patient against *Neisseria meningitidis (see section on important safety information)*

- **Inform and educate** your patient being treated with ULTOMIRIS® about the risk of meningococcal infection *(see section on important safety information)*
- Explain why patients must be vaccinated before starting the treatment and will need to be revaccinated
- Explain why they should be on antibiotic prophylaxis if **ULTOMIRIS®** is initiated less than 2 weeks before vaccination or they are unable to be vaccinated
- Provide a Patient Safety Card to patients and explain that they must carry it at all times while on Ultomiris and for 8 months after last dose and must show it to healthcare professionals
- Train them to recognise signs and symptoms of meningococcal infection and to seek medical attention

- Make sure your patient treated with **ULTOMIRIS®** understands the information given

- Warn them about the risk of interrupting treatment (see section on treatment discontinuation)

- Plan and agree with the patient treated with **ULTOMIRIS®** on a dosing appointment schedule

To help you start your patient on ULTOMIRIS®, you will be provided a “starter’s kit” to give to each patient treated with ULTOMIRIS® to give important information about this treatment.

THIS STARTER’S KIT COMPRISES:

- **PNH Patient information brochure:** provides your patient with information regarding PNH, ULTOMIRIS®, the potential side effects of the treatment, and safety warnings.

- **Patient Safety Card:** specifies that the person carrying it is under ULTOMIRIS® treatment; the physician’s name and telephone number are also included. Your patient must carry this card at all times while on Ultomiris and for 8 months after last dose.

DOSING & ADMINISTRATION[1]

ULTOMIRIS® Adult dosing schedule

The recommended dosing regimen for adult patients (≥ 18 years of age) 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*.

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

For patients switching from eculizumab to ravulizumab, a loading dose of ravulizumab should be administered 2 weeks after the last eculizumab infusion, as shown in *Table 1*.

Administer ULTOMIRIS® at the recommended dosing interval or within 7 days before or after scheduled dosing time point.

Fixed dose on time is critical to control chronic, complement-mediated haemolysis
No dosing adjustments recommended based on age, gender, race, or renal insufficiency
Premedications are not routinely required

Administering ULTOMIRIS® to patients[1]

ULTOMIRIS® is supplied as a 300 mg single-use vial.

ULTOMIRIS® should only be administered as an IV infusion and must be diluted to a final concentration of **5 mg/mL** prior to administration. The diluted solution is clear to translucent with a slight whitish color and should be practically free of any particles.

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION

- If diluted solution is refrigerated, warm to room temperature (18°C- 25°C) only by exposure to ambient air. Do not microwave
- Administer as an IV infusion using a calibrated infusion pump and 0.2 or 0.22 µm filter. Please refer to *Table 2* for minimum infusion time.
- It is not necessary to protect diluted solution from light during administration.

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)

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

ULTOMIRIS® should be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological disorders.

Headaches

During clinical trials some patients experienced a headache following infusion with ULTOMIRIS®. Headaches tended to occur following the first one or two infusions, after which they resolved. Headaches generally responded to simple analgesia and did not require prophylactic treatment.

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TREATMENT DISCONTINUATION[1]

Since PNH is a chronic disease, ULTOMIRIS® is intended to be an ongoing therapy.[2]

Patients who start ULTOMIRIS® should continue receiving ULTOMIRIS®, even if they feel better.

However, patients who discontinue treatment with ULTOMIRIS® should be **monitored for signs and symptoms of serious intravascular haemolysis** and other reactions **for at least 16 weeks.**

There is SERIOUS HAEMOLYSIS when[1]:

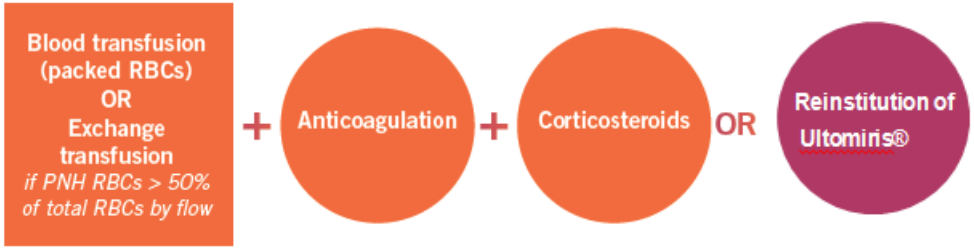
Serum LDH > pre-treatment LDH

+

Any of the following criteria:

- PNH clone size decrease of > 25% in 1 week or less
- Hb < 5 g/dL
- Hb decrease of > 4 g/dL in 1 week or less
- Angina
- Change in mental status
- Serum creatinine increase of 50%
- Thrombosis

IF SERIOUS HAEMOLYSIS OCCURS, consider the following procedures/treatment:



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SPECIAL HANDLING AND STORAGE[1]

- Store in a refrigerator (2°C– 8°C), in the original package to protect from light. **Do not freeze.**
- Reconstitution and dilution should be performed in accordance with good practices rules, particularly for the respect of asepsis.
- 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.

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Reporting of side effects

Side effects can be reported to the 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