Physician's guide to prescribing for patients with refractory generalised Myasthenia Gravis (gMG)

This document was last approved in March 2021 by the Israeli Ministry of Health (MOH)

WHAT IS SOLIRIS®? [1]

SOLIRIS® is a recombinant humanised monoclonal antibody targeting the complement protein C5.

Eculizumab, the active ingredient in SOLIRIS®, is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Eculizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms, initiation of immune response (both humoral and cellular) and clearance of immune complexes.

SOLIRIS® is a first-in-class, humanised monoclonal antibody targeting C5

- SOLIRIS® binds to C5 with high affinity
- SOLIRIS® blocks activation of terminal complement components C5a and C5b-9
- SOLIRIS® preserves the proximal pathway defense mechanisms

In refractory gMG patients, uncontrolled terminal complement activation and the resulting complement-mediated morphologic damage to the post-synaptic membrane of the neuromuscular junction are blocked with SOLIRIS® treatment. In refractory gMG, administration of SOLIRIS® resulted in a rapid and sustained effect on symptoms and signs of refractory gMG.

SOLIRIS® INDICATIONS [1]

SOLIRIS® (eculizumab) is indicated in adults for the treatment of:

- **Refractory generalised Myasthenia Gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive.**

SOLIRIS® (eculizumab) is also indicated in:

- adults for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in patients who are anti-aquaporin-4 antibody-positive with a relapsing course of the disease.
- adults and children for the treatment of:
  - Paroxysmal Nocturnal Haemoglobinuria (PNH). Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history.
  - Atypical Haemolytic Uremic Syndrome (aHUS).

IMPORTANT SAFETY INFORMATION [1]

Due to its mechanism of action, the use of SOLIRIS® increases the risk of severe infection and sepsis, especially meningococcal infection (*Neisseria meningitidis*) for the patient.

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

- **Provide** your patients with a vaccination and prophylactic antibiotics as explained below:

  - **Vaccinate** your patients with a meningococcal vaccine at least 2 weeks prior to receiving SOLIRIS® unless the risk of delaying SOLIRIS® therapy outweighs the risks of developing a meningococcal infection.
  - Vaccines against serogroups A, C, Y, W 135 and B (where available) are recommended.
  - Vaccination or revaccination may further activate complement and, as a result, patients with complement-mediated diseases, including PNH, aHUS, refractory gMG, and NMOSD may experience increased signs and symptoms of their underlying disease, such as haemolysis (PNH), TMA (aHUS), MG exacerbation (refractory gMG) or relapse (NMOSD). Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.
  - Vaccinate according to current national vaccination guidelines for vaccine use.
  - Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents. Cases of serious or fatal meningococcal infections have been reported in Soliris-treated patients. Sepsis is a common presentation of meningococcal infections in patients treated with Soliris.
  - All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary.
  - Patients should be informed of these signs and symptoms and steps taken to seek medical care immediately. Physicians must discuss the benefits and risks of Soliris therapy with patients and provide them with a patient information brochure and a patient safety card.
  - In patients for whom the vaccine is contra-indicated and in patients treated with SOLIRIS® 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. Some antibiotics have been associated with worsening of MG symptoms.

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

- **Provide a refractory gMG Patient brochure. Explain the brochures** to patients being treated with **SOLIRIS®** in order to increase their awareness of potential serious infections and the relevant signs and symptoms which include:

  - Headache with nausea or vomiting
  - Headache with a stiff neck or back
  - Fever
  - Rash
  - Confusion
  - Severe muscle ache combined with flu-like symptoms
  - Sensitivity to light

- **Provide a Patient Safety Card** to patients being treated with **SOLIRIS®** and explain that they must carry it at all times 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:

Due to its mechanism of action, SOLIRIS® therapy should be administered with caution to patients with active systemic infections (particularly due to Neisseria and encapsulated bacteria). Serious infections with Neisseria species (other than Neisseria meningitidis), including disseminated gonococcal infections, have been reported.

Patients should be provided with information from the Package Leaflet to increase their awareness of signs and symptoms of potential serious infections and the signs and symptoms of them. Physicians should advise patients about gonorrhoea prevention.

SOLIRIS® SAFETY PROFILE [1]

Contraindications

SOLIRIS® therapy must not be initiated in refractory gMG patients:

- With unresolved serious *Neisseria meningitidis* infection
- 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 refractory gMG patients has not been studied and is a subject of further clinical development.

Renal impairment:

No dose adjustment is required for patients with renal impairment.

Hepatic impairment:

The safety and efficacy of SOLIRIS® has not been studied in patients with hepatic impairment.

Elderly population:

No overall differences in safety were reported between elderly (≥ 65 years) and younger refractory gMG patients (< 65 years).

Infusion Reactions:

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

Patients should be monitored for one hour following infusion. If an adverse event occurs during the administration of SOLIRIS®, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time may not exceed two hours in adults.

In clinical trials, no refractory gMG patients experienced an infusion reaction requiring discontinuation of SOLIRIS®.

Immunogenicity:

Infrequent antibody responses have been detected in SOLIRIS®-treated patients across clinical studies. So far, no antibody responses have been detected in refractory gMG patients. There has been no observed correlation of antibody development to clinical response or adverse events.

Aspergillus Infection

Cases of *Aspergillus* Infections, some of them fatal, have been reported in SOLIRIS® treated patients. Underlying risk factors such as, long term steroid use, immunosuppressive treatments, severe pancytopenia, exposure to construction or demolition sites, and pre–existing lung impairment or *Aspergillus* infection should be considered. If one of the above risk factors is identified before starting treatment with

SOLIRIS®, appropriate measures to mitigate the risk of *Aspergillus* infection are advisable.

Immunosuppressant Therapies:

Patients in refractory gMG clinical trials continued treatment with immunosuppressant and anticholinesterase therapies while on Soliris treatment. When immunosuppressant and anticholinesterase therapies are decreased or discontinued, patients should be monitored closely for signs of disease exacerbation.

STARTING YOUR PATIENT ON SOLIRIS® [1]

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

- Inform and educate your patient being treated with **SOLIRIS®** about the risk of meningococcal infection and other serious infections:
  - *Explain why patients must be vaccinated before starting the treatment and will need to be revaccinated*
  - *Train them to recognise signs and symptoms of serious potential infection (or sepsis) and to seek medical advice*
  - *Provide a Patient Safety Card to patients and explain that they must carry it at all times and must show it to healthcare professionals.*
- Make sure your patient being treated with **SOLIRIS®** understand the information given
- Warn them about the risk of interrupting treatment (see paragraph on treatment discontinuation)
- Plan and agree with the patient being treated with **SOLIRIS®** on a dosing appointment schedule
- Vaccinate your patient against *Neisseria meningitidis* at least 2 weeks before the first SOLIRIS® infusion unless the risk of delaying SOLIRIS®s therapy or the risk of complement activation amplified by vaccination outweighs the risks of developing a meningococcal infection.
- Provide your patient with prophylactic antibiotics as explained above

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

This **starter’s kit** comprises:

- **Refractory gMG Patient information brochure:** provides your patient with information regarding refractory gMG, SOLIRIS®, the potential side effects of the treatment, and safety warnings.

- **Patient Safety Card:** specifies that the person carrying it is under SOLIRIS® treatment; physician's name and telephone number are also indicated. Your patient must carry this card at all times.

DOSING & ADMINISTRATION [1]

Dosing schedule

Adults

The dosing regimen (Table 1) consists of a **4-week initial phase** followed by **a maintenance phase**.

Dosing Schedule (Adults)										
Pre treatment		**Initial Phase**				**Maintenance Phase**				
≥ 2 weeks before induction	**Week**	1	2	3	4	5	6	7	8	9 and every 2 weeks thereafter
Neisseria meningitidis vaccination	**Dose of SOLIRIS® (mg)**	900	900	900	900	1200	-	1200	-	1200
	No. of vials	3	3	3	3	4	-	4	-	4

Dose within ± 2 days

Table 1: Dosing Schedule

- The diluted solution of SOLIRIS® should be administered by intravenous infusion over 25 to 45 minutes
- The total infusion time may not exceed two hours in adults

Administering SOLIRIS® to patients [1]

Pre-medications are not routinely required.

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

SOLIRIS® 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 a clear, colourless liquid 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—25°C) only by exposure to ambient air.
- Administer as an IV infusion **over 25 to 45 minutes** via gravity feed, a syringe-type pump, or an infusion pump.
  The total infusion time may not exceed 2 hours **in adults**
- It is not necessary to protect diluted solution from light during administration.

SOLIRIS® should be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with neuromuscular diseases.

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

TREATMENT DISCONTINUATION [1]

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

Use of SOLIRIS® in refractory gMG treatment has been studied in the setting of chronic administration. Patients that discontinue Soliris treatment should be carefully monitored for signs and symptoms of disease exacerbation.

SPECIAL HANDLING AND STORAGE [1]

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

Store in the original package in order to protect from light.
SOLIRIS® vials in the original package may be removed from refrigerated storage for only one single period of up to 3 days. At the end of this period, the product can be put back in the refrigerator.

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

REFERENCES

1. SOLIRIS® (eculizumab) Summary of Product Characteristics, as approved by the Israeli MoH.
2. Bilukha OO, Rosenstein N, for the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC). Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2005;54:1-21.

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

IMPORTANT INFORMATION
VACCINATION/Prophylaxis antibiotic CERTIFICATE

In order to minimize the risk of inappropriate use of SOLIRIS®, the Decision of the European Commission and the follow-up measures agreed by the CHMP require that drug distribution by Alexion will only be possible after written confirmation that the patient has effectively received meningococcal vaccination and/or antibiotic prophylaxis.

Therefore, together with this Guide you received a Vaccination/Prophylaxis antibiotic Certificate, which must be filled in for each new patient and sent to Alexion Pharma Israel (by fax:
+972-3-9264237, or Email: RMP@neopharmgroup.com), together with an order for SOLIRIS® for a new patient.

Alexion Pharma Israel will not be able to process any orders for patients for which we have not received the Vaccination/Prophylaxis antibiotic Certificate.

We therefore ask you to enter the patient code and the birthdate of the patient for whom the drug is purchased on any future orders for SOLIRIS®, to be able to verify the correspondence with the Vaccination/Prophylaxis antibiotic Certificate.

NEOPHARM ISRAEL
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SOLIRIS®
(eculizumab)

ALEXION
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120-FEB-2022