Physician‘s guide to prescribing for patients with aHUS

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

WHAT IS SOLIRIS®? [1]

SOLIRIS® is first-in-class recombinant humanised monoclonal antibody targeting the complement protein C5.

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

Atypical haemolytic uremic syndrome (aHUS) is a genetic disease where patients are unable to regulate the complement system, a part of the natural immune system which is always active and normally highly regulated. In aHUS chronic uncontrolled complement activation leads to ongoing platelet activation, endothelial cell damage and widespread inflammation and thrombosis throughout the body, a process known as systemic thrombotic microangiopathy (systemic TMA). Systemic TMA leads to damage and failure of many organs including the brain, heart, kidney and gastrointestinal system.

By blocking terminal complement activation SOLIRIS® reduces chronic systemic TMA that results from uncontrolled terminal complement activation in aHUS. Soliris specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (a potent anaphylatoxin) and preventing the generation of the lytic terminal complement complex C5b-9. Therefore, SOLIRIS® inhibits/controls terminal complement mediated thrombotic microangiopathy and prevents the damage caused by widespread inflammation and thrombosis.

SOLIRIS® INDICATIONS [1]

SOLIRIS® (eculizumab) is indicated in adults and children for the treatment of patients with atypical haemolytic uremic syndrome (aHUS).

Soliris is also indicated in:

- adults and children for the treatment of patients with 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.
- adults for the treatment of refractory generalised Myasthenia Gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive.
- 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.

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

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 prophylactic care as explained below:
  - **Vaccinate** your patient against *Neisseria meningitidis* 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, W135 and B (where available) are recommended.
  - Vaccination 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 young children for whom there is no vaccine recommended or available for use, 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.
  - Vaccinate patients less than 18 years against *Haemophilus influenza and pneumococcal infections* according to national vaccination guidelines at least 2 weeks prior to initiation of Soliris therapy and strictly adhere to the national vaccination recommendations for each age group.

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

- **Provide an aHUS Patient/Parent brochure** (to patients and to parents of children and adolescents), an **aHUS Parent brochure** (to parents of young children). **Explain them** to patients and/or parents/legal guardians of children 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 and/or parents/legal guardians of children 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.**

Train the parents/legal guardians of new-borns and infants to be aware that the typical symptoms of headache, fever, and neck stiffness may be hard to detect, so to train them to be aware of other symptoms in babies including inactivity, irritability, vomiting, and poor feeding.

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.

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

SOLIRIS® SAFETY PROFILE [1]

Contraindications

SOLIRIS® therapy must not be initiated in aHUS patients:

- With unresolved *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 patients with aHUS treated with Soliris observed in a retrospective study appeared similar to that observed in adult/adolescent aHUS patients. The most common (>10%) adverse events reported in paediatric patients were diarrhoea, vomiting, pyrexia, upper respiratory tract infection and headache.

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.

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 and adolescents (aged 12 years to under 18 years) and four hours in children aged less than 12 years.

Immunogenicity:

Infrequent antibody responses have been detected in Soliris-treated patients across all clinical studies.

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® (eculizumab) 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® (eculizumab), appropriate measures to mitigate the risk of Aspergillus infection are advisable.

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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 and/or parents/legal guardians of children being treated with **SOLIRIS®** about the risk of meningococcal infection and other serious infections:
  - *Explain why patients must receive prophylactic care as explained above*
  - *Train them to recognise signs and symptoms of serious potential infection (or Sepsis) and to seek medical advice*

  Explain what the Patient Safety Card is for and why they must carry it with them at all times

- Provide your patient with prophylactic antibiotics as explained above
- Make sure your patient and/or parents/legal guardians of children 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 and/or parents/legal guardians of children being treated with **SOLIRIS®** on a dosing appointment schedule
- Inform them about the **aHUS Registry** and how to participate

To help you start your patient on SOLIRIS®, you will be provided a "starter's kit", to give to each patient and/or parents/legal guardians of children being treated with **SOLIRIS®** to give important information about this treatment.

This **starter's kit** comprises:

- **aHUS Patient/Parent information brochure**: provides your patient and/or parents/legal guardians with information regarding aHUS, SOLIRIS®, the potential side effects of the treatment, and safety warnings. An **aHUS Parent information brochure** is available for parents or caregivers of young children.
- **Patient Safety Card**: specifies that the person carrying it is under SOLIRIS® treatment; shows the physician's name and telephone number. Your patient and/or parents/legal guardians of patients must carry this card at all times.

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DOSING & ADMINISTRATION [1]

Dosing schedule

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

Dosing Schedule											
Pre treatment	**Initial Phase**					**Maintenance Phase**					
≥ 2 weeks before induction:	Week	1	2	3	4	5	6	7	8	9	
Neisseria meningitidis vaccination for all patients	**SOLIRIS® Dose**									1200 mg and every 2 weeks thereafter	
	ADULTS	900 mg	900 mg	900 mg	900 mg	1200 mg	-	1200 mg	-		
	No. of vials	3	3	3	3	4	-	4	-	4	
Antibiotic treatment for patients who can't be vaccinated								Dose within ± 2 days			
Haemophilus influenza and pneumococcal vaccination for children	***CHILDREN***									1200 mg and every 2 weeks thereafter	
	> 40kg	900 mg	900 mg	900 mg	900 mg	1200 mg	-	1200 mg	-		
	No. of vials	3	3	3	3	4	-	4	-	4	
	30 to <40kg	600 mg	600 mg	900 mg	-	900 mg	-	900 mg	-	900mg and every 2 weeks thereafter	
	No. of vials	2	2	3		3	-	3	-	3	
	20 to <30kg	600 mg	600 mg	600 mg	-	600 mg	-	600 mg	-	600 mg and every 2 weeks thereafter	
	No. of vials	2	2	2		2	-	2	-	2	
	10 to <20kg	600 mg	300 mg	-	300 mg	-	300 mg		300 mg and every 2 weeks thereafter	-	
	No. of vials	2	1		1		1		1		
	5 to <10kg	300 mg	300 mg	-	-	300 mg	-	-	300 mg and every 3 weeks thereafter	-	
	No. of vials	1	1			1			1		

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 2 hours in adults and adolescents and 4 hours in children aged less than 12.**
- **Fixed dose on time** is critical to control thrombotic microangiopathy

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Administering SOLIRIS® to patients [1]

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°C- 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 and adolescents and 4 hours in children aged less than 12.**
- 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 renal disorders.

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.

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TREATMENT DISCONTINUATION [1]

Since aHUS is a chronic disease, SOLIRIS® is intended to be an **ongoing therapy**.[3]

Thrombotic microangiopathy (TMA) complications have been observed as early as 4 weeks and up to 127 weeks following discontinuation of Soliris treatment in some patients. Discontinuation of treatment should only be considered if medically justified.

If aHUS patients discontinue treatment with Soliris, they should be monitored closely for signs and symptoms of severe thrombotic microangiopathy complications. Monitoring may be insufficient to predict or prevent severe thrombotic microangiopathy complications in patients with aHUS after discontinuation of Soliris.

Severe TMA complications post discontinuation can be identified by (i) any two, or repeated measurement of any one, of the following: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during Soliris treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during Soliris treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during Soliris treatment; or (ii) any one of the following: a change in mental status or seizures; angina or dyspnoea; or thrombosis.

If severe thrombotic microangiopathy complications occur after Soliris discontinuation, consider reinstitution of Soliris treatment, supportive care with PE/PI, or appropriate organ-specific supportive measures including renal support with dialysis, respiratory support with mechanical ventilation or anticoagulation.

SPECIAL HANDLING AND STORAGE [1]

Store in a refrigerator (2°C– 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 with respect to asepsis.

REFERENCES

1. SOLIRIS® (eculizumab) Current Summary of Product Characteristics, as approved by the Israeli MoH.
2. Updated Recommendations for Use of Meningococcal Conjugate Vaccines — Advisory Committee on Immunization Practices (ACIP), 2010 MMWR. 2011; 60 (issue 3): 72-76
3. Loirat C et al. Eculizumab Efficacy and Safety in Patients With Atypical Hemolytic Uremic Syndrome (aHUS) Resistant to Plasma Exchange/Infusion. Presented at the XLVIII ERA-EDTA Congress, Prague; 23-26 June 2011.

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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

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 a completed Vaccination/Prophylaxis antibiotic Certificate.

We therefore ask you to enter the patient code and the birth date 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
NEOPHARM GROUP

SOLIRIS®
(eculizumab)

ALEXION
AstraZeneca Rare Disease

Alexion Pharma Israel
Hashiloah 6 St. Petah Tikva,
4951439

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