Soliris® (eculizumab): Physician’s guide to prescribing for patients with atypical haemolytic uraemic syndrome (aHUS)
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WHAT IS SOLIRIS®? 1

SOLIRIS® (eculizumab) is a first-in-class, recombinant, humanised monoclonal antibody targeting the complement protein C5.

Eculizumab, the active ingredient in SOLIRIS®, is a terminal complement inhibitor that specifically binds to C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. SOLIRIS® 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® binds to C5 with high affinity
- SOLIRIS® blocks activation of terminal complement components C5a and C5b-9
- SOLIRIS® preserves the proximal complement pathway defense mechanisms

Atypical haemolytic uraemic syndrome (aHUS) is a genetic disease affecting 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. 2

In aHUS patients, uncontrolled terminal complement activation and the resulting complement-mediated TMA are blocked by SOLIRIS®.

SOLIRIS® INDICATIONS 1

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

SOLIRIS® is also indicated in:

- 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.
- Adults for the treatment of refractory generalised myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive.
IMPORTANT SAFETY INFORMATION

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 **vaccination against *Neisseria meningitidis* 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, W135 and B (where available) are recommended
  - Vaccination may further activate complement. As a result, patients with complement-mediated diseases, including PNH, aHUS and refractory gMG may experience increased signs and symptoms of their underlying disease, such as haemolysis (PNH), TMA (aHUS) or gMG exacerbation (refractory gMG). Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.
  - Vaccinate according to current national vaccination guidelines for vaccine use.
  - 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 influenzae* 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.

- **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), or an aHUS Parent brochure (to parents of young children). **Explain the brochures** 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 newborns and infants to be aware that the typical symptoms of headache, fever, and neck stiffness may be hard to detect: so 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 encapsulated bacteria).

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 (aged 2 months to <18 years) 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 event reported in paediatric patients was 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.

In clinical trials, no aHUS, PNH or refractory gMG patients experienced an infusion reaction which required discontinuation of SOLIRIS®.
**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®-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.

**STARTING YOUR PATIENT ON SOLIRIS®**

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 be vaccinated before starting 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 with them at all times and show it to healthcare professionals*
- **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
- **Provide** your patient with prophylactic antibiotics as explained above
- **Vaccinate** your patient against *Neisseria meningitidis* at least 2 weeks before the first SOLIRIS® infusion unless the risk of delaying SOLIRIS® therepay or the risk of complement activation amplified by vaccination outweighs the risks of developing a meningococcal infection

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; physician’s name and telephone number are also indicated. Your patient and/or parents/legal guardians of patients must carry this card at all times.
DOSING & ADMINISTRATION

Dosing schedule

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

<table>
<thead>
<tr>
<th>Pre Treatment</th>
<th>Initial Phase</th>
<th>Maintenance Phase</th>
</tr>
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<tbody>
<tr>
<td>≥ 2 weeks before induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neisseria meningitidis vaccination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antibiotic treatment for patients who can’t be vaccinated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOLIRIS® dose</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>Week</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>SOLIRIS® dose by child’s weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>900 mg</td>
<td>900 mg</td>
</tr>
<tr>
<td>No. of vials</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>30 to &lt;40 kg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>No. of vials</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>20 to &lt;30 kg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>No. of vials</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>10 to &lt;20 kg</td>
<td>600 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>No. of vials</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5 to &lt;10 kg</td>
<td>300 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>No. of vials</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Supplemental dosing of SOLIRIS® is required in the setting of concomitant PE/PI (plasmapheresis or plasma exchange, or fresh frozen plasma infusion).

<table>
<thead>
<tr>
<th>Type of Plasma Intervention</th>
<th>Most recent SOLIRIS® dose</th>
<th>Supplemental SOLIRIS® dose with each PE/PI intervention</th>
<th>Timing of supplemental SOLIRIS® dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmapheresis or plasma exchange</td>
<td>300 mg</td>
<td>300 mg per each plasmapheresis or plasma exchange session</td>
<td>Within 60 minutes after each plasmapheresis or plasma exchange</td>
</tr>
<tr>
<td></td>
<td>≥600 mg</td>
<td>600 mg per each plasmapheresis or plasma exchange session</td>
<td></td>
</tr>
<tr>
<td>Fresh frozen plasma infusion</td>
<td>≥300 mg</td>
<td>300 mg per infusion of fresh frozen plasma</td>
<td>60 minutes prior to each infusion of fresh frozen plasma</td>
</tr>
</tbody>
</table>

• The diluted solution of SOLIRIS® should be administered by intravenous infusion over 25 to 45 minutes in adults and 1-4 hours in paediatric patients. The total infusion time may not exceed 2 hours in adults and adolescents (aged 12 years to under 18 years) and 4 hours in children aged less than 12 years.

• Timely administration of recommended doses is critical to control thrombotic microangiopathy.

ADMINISTERING SOLIRIS® TO PATIENTS

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.

ADMINISTER AS AN IV INFUSION ONLY

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 in adults and 1–4 hours in paediatric patients, 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. Headaches generally responded to simple analgesia and did not require prophylactic treatment.

TREATMENT DISCONTINUATION 1

Since aHUS 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.

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.

Monitoring after discontinuations

If aHUS patients discontinue treatment with SOLIRIS®, they should be monitored closely for signs and symptoms of severe TMA complications. Monitoring may be insufficient to predict or prevent severe TMA 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 TMA 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 (2–8°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.
REPORTING ADVERSE DRUG REACTIONS

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare Professionals are asked to report any suspected adverse reactions.

Ireland
HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel: +3531 6764971; Fax: +353 1 6762517. Website: www.hpra.ie Email: medsafety@hpra.ie.

Adverse events should also be reported to Alexion Pharma UK Ltd on 1800 936 544 or uk.adverseevents@alexion.com.

UK
Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.mhra.gov.uk.

Adverse events should also be reported to Alexion Pharma UK Ltd on email: uk.adverseevents@alexion.com or call: 0800 321 3902.

MORE INFORMATION

For more information about SOLIRIS® contact:

Medicalinformation.uk@alexion.com Tel: UK: 0800 689 1592 / Ireland: 1800936 537

Alexion funds a Home Healthcare service, which is available to all patients prescribed with SOLIRIS®.

For more details, please contact your local Alexion office via customeroperationsuk@alexion.com or Tel: 0800 130 0212.

REFERENCES

1. SOLIRIS® (eculizumab) Current Summary of Product Characteristics. Alexion Europe SAS.
IMPORTANT INFORMATION

VACCINATION/Prophylaxis antibiotic CERTIFICATE

In order to minimise 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, by fax on 0800 633 5145 (UK) or 1800 995 100 (EI) or by email: customeroperations@alexion.com, together with an order for SOLIRIS® for a new patient.

Alexion 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.