SOLIRIS®
(eculizumab)

1. NAME OF THE MEDICINAL PRODUCT

SOLIRIS 300 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Eculizumab is a humanised monoclonal ($IgG_{2/4\kappa}$) antibody produced in NS0 cell line by recombinant DNA technology.

2.2 Qualitative and quantitative composition

One vial of 30 ml contains 300 mg of eculizumab (10 mg/ml).
After dilution, the final concentration of the solution to be infused is 5 mg/ml.
Excipients with known effect: Sodium (5mmol per vial)
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for Solution for Infusion.
Clear, colorless, pH 7.0 solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SOLIRIS is 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 (see section 5.1).
- Atypical Haemolytic Uremic Syndrome (aHUS) (see section 5.1).

4.2 Posology and method of administration

SOLIRIS must be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological and/or renal disorders.

Posology

Adult patients

In Paroxysmal Nocturnal Haemoglobinuria (PNH):

The PNH dosing regimen for adult patients (≥18 years of age) consists of a 4-week initial phase followed by a maintenance phase:

- Initial phase: 600 mg of SOLIRIS administered via a 25 - 45-minute intravenous infusion every week for the first 4 weeks.
- Maintenance phase: 900 mg of SOLIRIS administered via a 25 - 45-minute intravenous infusion for the fifth week, followed by 900 mg of SOLIRIS administered via a 25 – 45-minute intravenous infusion every 14 ± 2 days (see section 5.1).

In Atypical Haemolytic Uremic Syndrome (aHUS):

The aHUS dosing regimen for adult patients (≥ 18 years of age) consists of a 4-week initial phase followed by a maintenance phase:

- Initial phase: 900 mg of SOLIRIS administered via a 25 - 45-minute intravenous infusion every week for the first 4 weeks.
- Maintenance phase: 1,200 mg of SOLIRIS administered via a 25 - 45-minute intravenous infusion for the fifth week, followed by 1,200 mg of SOLIRIS administered via a 25 - 45-minute intravenous infusion every 14 ± 2 days (see section 5.1).

Paediatric patients in PNH and aHUS:

Paediatric PNH and aHUS patients with body weight ≥ 40kg are treated with the adult dosing recommendations, respectively.

In paediatric PNH and aHUS patients with body weight below 40 kg, the SOLIRIS dosing regimen consists of:

Patient Body Weight	Initial Phase	Maintenance Phase
30 to <40 kg	600 mg weekly x 2	900 mg at week 3; then 900 mg every 2 weeks
20 to <30 kg	600 mg weekly x 2	600 mg at week 3; then 600 mg every 2 weeks
10 to <20 kg	600 mg weekly x 1	300 mg at week 2; then 300 mg every 2 weeks
5 to <10 kg	300 mg weekly x 1	300 mg at week 2; then 300 mg every 3 weeks

SOLIRIS has not been studied in patients with PNH who weigh less than 40kg. The posology of SOLIRIS for PNH patients less than 40kg weight is based on the posology used for patients with aHUS and who weigh less than 40kg.

For adults and paediatric aHUS patients supplemental dosing of SOLIRIS is required in the setting of concomitant PE/PI (plasmapheresis or plasma exchange, or fresh frozen plasma infusion):

Type of Plasma Intervention	Most Recent SOLIRIS Dose	Supplemental SOLIRIS Dose with Each PE/PI Intervention	Timing of Supplemental SOLIRIS Dose
Plasmapheresis or	300 mg	300 mg per each plasmapheresis or plasma	Within 60 minutes after each

Type of Plasma Intervention	Most Recent SOLIRIS Dose	Supplemental SOLIRIS Dose with Each PE/PI Intervention	Timing of Supplemental SOLIRIS Dose
plasma exchange		exchange session	plasmapheresis or plasma exchange
	≥600 mg	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	≥300 mg	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

Treatment Monitoring

aHUS patients should be monitored for signs and symptoms of thrombotic microangiopathy (TMA) (refer to section 4.4 aHUS Laboratory Monitoring).

SOLIRIS treatment is recommended to continue for the patient's lifetime, unless the discontinuation of SOLIRIS is clinically indicated (see section 4.4).

Method of administration

Do not administer as an intravenous push or bolus injection. SOLIRIS should only be administered via intravenous infusion as described below.

For instructions on dilution of the medicinal product before administration, see section 6.6.

The diluted solution of SOLIRIS should be administered by intravenous infusion over 25 – 45 minutes in adults and 1-4 hours in paediatric patients via gravity feed, a syringe-type pump, or an infusion pump. It is not necessary to protect the diluted solution of SOLIRIS from light during administration to the patient.

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.

Elderly

SOLIRIS may be administered to patients aged 65 years and over. There is no evidence to suggest that any special precautions are needed when older people are treated – although experience with SOLIRIS in this patient population is still limited.

Renal impairment

No dose adjustment is required for patients with renal impairment (see section 5.1).

Hepatic impairment

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

4.3 Contraindications

Hypersensitivity to eculizumab, murine proteins or to any of the excipients listed in section 6.1.

SOLIRIS therapy must not be initiated in patients (see section 4.4):

- 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.

4.4 Special warnings and precautions for use

SOLIRIS is not expected to affect the aplastic component of anaemia in patients with PNH.

Meningococcal Infection

Due to its mechanism of action, the use of SOLIRIS increases the patient's susceptibility to meningococcal infection (*Neisseria meningitidis*). Meningococcal disease due to any serogroup may occur. To reduce the risk of infection, all patients must be vaccinated at least 2 weeks prior to receiving SOLIRIS unless the risk of delaying SOLIRIS therapy outweighs the risks of developing a meningococcal infection. Patients who initiate SOLIRIS treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y, W135 and B where available, are recommended in preventing the commonly pathogenic meningococcal serotypes. Patients must receive vaccination according to current national vaccination guidelines for vaccination use.

Vaccination may further activate complement. As a result, patients with complement-mediated diseases, including PNH and aHUS, may experience increased signs and symptoms of their underlying disease, such as haemolysis (PNH) or TMA (aHUS). Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

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 (see section 4.8). All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with 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 (see Package Leaflet for a description).

Other Systemic Infections

Due to its mechanism of action, SOLIRIS therapy should be administered with caution to patients with active systemic infections. Patients may have increased susceptibility to infections, especially with *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 Patient Leaflet to increase their awareness of potential serious infections and the signs and symptoms of them. Physicians should advise patients about gonorrhoea prevention.

Infusion Reactions

Administration of SOLIRIS may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis), though immune system disorders within 48 hours of SOLIRIS administration did not differ from placebo treatment in PNH, aHUS and other studies conducted with SOLIRIS. In clinical trials, no PNH or aHUS patients experienced an infusion reaction which required discontinuation of SOLIRIS. SOLIRIS administration should be interrupted in all patients experiencing severe infusion reactions and appropriate medical therapy administered.

Immunogenicity

Infrequent antibody responses have been detected in SOLIRIS treated patients across all clinical studies. In PNH placebo-controlled studies low antibody responses have been reported with a frequency (3.4%) similar to that of placebo (4.8%).

In patients with aHUS treated with SOLIRIS, antibodies to SOLIRIS were detected in 3/100 (3%) by the ECL bridging format assay. 1/100 (1%) aHUS patients had low positive values for neutralizing antibodies.

There has been no observed correlation of antibody development to clinical response or adverse events.

Immunization

Prior to initiating SOLIRIS therapy, it is recommended that PNH and aHUS patients initiate immunizations according to current immunization guidelines. Additionally, all patients must be vaccinated against meningococcal infections at least 2 weeks prior to receiving SOLIRIS unless the risk of delaying SOLIRIS therapy outweighs the risks of developing a meningococcal infection. Patients who initiate SOLIRIS treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y, W135 and B where available are recommended in preventing the commonly pathogenic meningococcal serogroups (see Meningococcal Infection).

Patients less than 18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections, and strictly need to adhere to the national vaccination recommendations of each age group.

Vaccination may further activate complement. As a result, patients with complement-mediated diseases, including PNH and aHUS, may experience increased signs and symptoms of their underlying disease, such as haemolysis (PNH) or TMA (aHUS). Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

Anticoagulant therapy

Treatment with SOLIRIS should not alter anticoagulant management.

PNH Laboratory Monitoring

PNH patients should be monitored for signs and symptoms of intravascular haemolysis, including serum lactate dehydrogenase (LDH) levels. PNH patients receiving SOLIRIS

therapy should be similarly monitored for intravascular haemolysis by measuring LDH levels, and may require dose adjustment within the recommended 14±2 day dosing schedule during the maintenance phase (up to every 12 days).

aHUS Laboratory Monitoring

aHUS patients receiving SOLIRIS should be monitored for thrombotic microangiopathy by measuring platelet counts, serum LDH levels and serum creatinine and may require dose adjustment within the recommended 14 ± 2-day dosing schedule during the maintenance phase (up to every 12 days).

Treatment Discontinuation for PNH

If PNH patients discontinue treatment with SOLIRIS, they should be monitored for signs and symptoms of serious intravascular haemolysis. Serious haemolysis is identified by serum LDH levels greater than the pre-treatment level, along with any of the following: greater than 25% absolute decrease in PNH clone size (in the absence of dilution due to transfusion) in one week or less; a haemoglobin level of <5 g/dL or a decrease of >4 g/dL in one week or less; angina; change in mental status; a 50% increase in serum creatinine level; or thrombosis. Monitor any patient who discontinues SOLIRIS for at least 8 weeks to detect serious haemolysis and other reactions.

If serious haemolysis occurs after SOLIRIS discontinuation, consider the following procedures/treatments: blood transfusion (packed RBCs), or exchange transfusion if the PNH RBCs are >50% of the total RBCs by flow cytometry; anticoagulation; corticosteroids; or reinstitution of SOLIRIS. In PNH clinical studies, 16 patients discontinued the SOLIRIS treatment regimen. Serious haemolysis was not observed.

Treatment Discontinuation for aHUS

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.

In aHUS clinical studies, 61 patients (21 paediatric patients) discontinued SOLIRIS treatment with a median follow-up period of 24 weeks. Fifteen severe thrombotic microangiopathy (TMA) complications in 12 patients were observed following treatment discontinuation, and 2 severe TMA complications occurred in an additional 2 patients that received a reduced dosing regimen of SOLIRIS outside of the approved dosing regimen (See section 4.2). Severe TMA complications occurred in patients regardless of whether they had an identified genetic mutation, high risk polymorphism or auto-antibody. Additional serious medical complications occurred in these patients including severe worsening of kidney function, disease-related hospitalization and progression to end stage renal disease requiring dialysis. Despite SOLIRIS re-initiation following discontinuation, progression to end stage renal disease occurred in one patient.

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 thrombotic microangiopathy 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.

Educational Materials

All physicians who intend to prescribe SOLIRIS must ensure they are familiar with the physician's guide to prescribing. Physicians must discuss the benefits and risks of SOLIRIS therapy with patients and provide them with a Patient/Parent Information Brochure and a Patient Safety Card.

Patients should be instructed that if they develop fever, headache accompanied with fever and/or stiff neck or sensitivity to light, they should immediately seek medical care as these signs may be indicative of meningococcal infection.

Excipients

This medicinal product contains 5 mmol sodium per vial. It should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Chronic intravenous human immunoglobulin (IVIg) treatment may interfere with the endosomal neonatal Fc receptor (FcRn) recycling mechanism of monoclonal antibodies such as eculizumab and thereby decrease serum eculizumab concentrations. Drug interaction studies have not been conducted with eculizumab in patients treated with IVIg.

4.6 Fertility, pregnancy and lactation

The use of adequate contraception to prevent pregnancy and for at least 5 months after the last dose of treatment with eculizumab should be considered for women of childbearing potential.

Pregnancy

There are no well-controlled studies in pregnant women treated with eculizumab. Data on a limited number of pregnancies exposed to eculizumab (less than 300 pregnancy outcomes) indicate there is no increased risk of foetal malformation or foetal-neonatal toxicity. However, due to the lack of well-controlled studies, uncertainties remain. Therefore, an individual risk benefit analysis is recommended before starting and during treatment with eculizumab in pregnant women. Should such a treatment be considered necessary during pregnancy, a close maternal and foetal monitoring according to local guidelines is recommended.

Animal reproduction studies have not been conducted with eculizumab (see section 5.3)

Human IgG are known to cross human placental barrier, and thus eculizumab may potentially cause terminal complement inhibition in the foetal circulation. Therefore, SOLIRIS should be given to a pregnant woman only if clearly needed.

Breastfeeding

No effects on the breastfed newborn / infant are anticipated as limited data available suggest that eculizumab is not excreted into human breast milk. However, due to the limitations of the available data, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for eculizumab and any potential adverse effects on the breastfed child from eculizumab or from the underlying maternal condition.

Fertility

No specific study of eculizumab on fertility has been conducted.

4.7 Effects on ability to drive and use machines

SOLIRIS has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Supportive safety data were obtained from 29 completed and one ongoing clinical studies that included 1,407 patients exposed to eculizumab in ten disease populations, including PNH and aHUS. The most common adverse reaction was headache, (occurred mostly in the initial phase), and the most serious adverse reaction was meningococcal sepsis.

Tabulated list of adverse reactions

Table 1 gives the adverse reactions observed from spontaneous reporting and in eculizumab completed clinical trials, including PNH and aHUS studies. Adverse reactions reported at a very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) or rare (≥1/10,000 to <1/1,000) frequency with eculizumab, are listed by system organ class and preferred term. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse Reactions reported in 1,407 patients included in overall eculizumab clinical trials, including patients with PNH and aHUS, as well as from post-marketing experience.

MedDRA System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
Infection and infestations		Pneumonia, Upper respiratory tract infection, Nasopharyngitis, Urinary tract infection, Oral Herpes	Meningococcal infection[a], Sepsis, Septic shock, Peritonitis, Lower respiratory tract infection, Fungal infection, Viral infection, Bronchitis, Abscess, Cellulitis,	Aspergillus infection[b], Arthritis bacterial[b], Genitourinary tract gonococcal infection, Haemophilus influenzae

MedDRA System Organ Class	**Very Common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**
			Influenza, Gastrointestinal infection, Cystitis, Infection, Sinusitis, Tooth infection	infection, Impetigo, Gingivitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)				Malignant melanoma, Myelodysplastic syndrome
Blood and lymphatic system disorders		Leukopenia, Anaemia	Thrombocytopenia, Lymphopenia	Haemolysis*, Abnormal clotting factor, Red blood cell agglutination, Coagulopathy
Immune system disorders			Anaphylactic reaction, Hypersensitivity	
Endocrine disorders				Basedow's disease
Metabolism and nutrition disorders			Decreased appetite	
Psychiatric disorders		Insomnia	Depression, Anxiety, Mood swings	Abnormal dreams, Sleep disorder
Nervous system disorders	Headache	Dizziness, Dysgeusia, Tremor	Paraesthesia	Syncope
Eye disorders			Vision blurred	Conjunctival irritation
Ear and labyrinth disorders			Tinnitus, Vertigo	
Cardiac disorders			Palpitation	
Vascular disorders		Hypertension	Accelerated hypertension, Hypertension, Hypotension, Hot	Haematoma

MedDRA System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
			flush, Vein disorder	
Respiratory, thoracic and mediastinal disorders		Cough, Oropharyngeal pain,	Dyspnoea, Epistaxis, Throat irritation, Nasal congestion, Rhinorrhoea	
Gastrointestinal disorders		Diarrhoea, Vomiting, Nausea, Abdominal pain,	Constipation, Dyspepsia, Peritonitis, Abdominal distension,	Gastrooesophagal reflux disease, Gingival pain
Hepatobiliary disorders				Jaundice
Skin and subcutaneous tissue disorders		Rash, Pruritus, Alopecia,	Urticaria, Erythema, Petechiae, Hyperhidrosis, Dry skin	Dermatitis, Skin depigmentation
Musculoskeletal and connective tissue disorders		Arthralgia, Myalgia, Pain in extremity	Muscle spasms, Bone pain, Back pain, Neck pain, Joint swelling	Trismus
Renal and urinary disorders			Renal impairment, Dysuria	Haematuria
Reproductive system and breast disorders			Spontaneous penile erection, Menstrual disorder	
General disorders and administration site conditions		Pyrexia, Chills, Fatigue, Influenza like illness	Oedema, Chest discomfort, Asthenia, Chest pain, Infusion site pain,	Extravasation, Infusion site paraesthesia, Feeling hot
Investigations			Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Haematocrit decreased, Haemoglobin decreased	Coombs test positive[b]
Injury,			Infusion related	

MedDRA System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
poisoning and procedural complication			reaction	

*See paragraph Description of selected adverse reactions

[a] = Meningococcal infection includes the following group of PTs: Meningococcal sepsis, Meningococcal meningitis, Neisseria infection; [b] = Adverse reactions identified in post-marketing reports

Description of selected adverse reactions

In all clinical studies, including PNH and aHUS clinical trials, the most serious adverse reaction was meningococcal sepsis which is a common presentation of meningococcal infections in patients treated with SOLIRIS (see section 4.4).

Other cases of *Neisseria species* have been reported including sepsis with *Neisseria gonorrhoeae, Neisseria sicca/subflava, Neisseria spp* unspecified.

Antibodies to SOLIRIS were detected in 2% patients with PNH using an ELISA assay and 3% of patients with aHUS using the ECL bridging format assay. As with all proteins there is a potential for immunogenicity.

Cases of haemolysis have been reported in the setting of missed or delayed SOLIRIS dose in PNH clinical trials (see also section 4.4).

Cases of thrombotic microangiopathy complication have been reported in the setting of missed or delayed SOLIRIS dose in aHUS clinical trials (see also section 4.4).

Paediatric population

In children and adolescent PNH patients (aged 11 years to less than 18 years) included in the paediatric PNH Study M07-005, the safety profile appeared similar to that observed in adult PNH patients. The most common adverse reaction reported in paediatric patients was headache.

In aHUS patients, the safety profile in adolescents (patients aged 12 years to less than 18 years) is consistent with that observed in adults. In paediatric aHUS patients (aged 2 months to less than 18 years) included in the aHUS studies C08-002, C08-003, C09-001r and C10-003, the safety profile appeared similar to that observed in adult aHUS patients. The safety profiles in the different paediatric subsets of age appear similar.

Patients with other diseases

Safety Data from Other Clinical Studies

Supportive safety data were obtained in 13 clinical studies that included 856 patients exposed to eculizumab in other disease populations other than PNH and aHUS. There was an un-vaccinated patient diagnosed with idiopathic membranous glomerulonephropathy who experienced meningococcal meningitis. Adverse reactions reported in patients with disease other than PNH or aHUS were similar to those reported in patients with PNH or aHUS (see Table 1 above). No specific adverse reactions have emerged from these clinical studies.

Reporting of suspected adverse 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 via the national reporting system.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA25

SOLIRIS is a recombinant humanised monoclonal $IgG_{2/4k}$ antibody that binds to the human C5 complement protein and inhibits the activation of terminal complement. The SOLIRIS antibody contains human constant regions and murine complementarity-determining regions grafted onto the human framework light- and heavy-chain variable regions. SOLIRIS is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148kDa.

SOLIRIS is produced in a murine myeloma (NS0 cell line) expression system and purified by affinity and ion exchange chromatography. The bulk drug substance manufacturing process also includes specific viral inactivation and removal steps.

Mechanism of Action

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 opsonization of microorganisms and clearance of immune complexes.

In PNH patients, uncontrolled terminal complement activation and the resulting complement-mediated intravascular haemolysis are blocked with SOLIRIS treatment.

In most PNH patients, eculizumab serum concentrations of approximately 35 microgram/ml are sufficient for essentially complete inhibition of terminal complement-mediated intravascular haemolysis.

In PNH, chronic administration of SOLIRIS resulted in a rapid and sustained reduction in complement-mediated haemolytic activity.

In aHUS patients, uncontrolled terminal complement activation and the resulting complement-mediated thrombotic microangiopathy are blocked with SOLIRIS treatment.

All patients treated with SOLIRIS when administered as recommended demonstrated rapid and sustained reduction in terminal complement activity. In all aHUS patients, eculizumab serum concentrations of approximately 50 - 100 microgram/ml are sufficient for essentially complete inhibition of terminal complement activity.

In aHUS, chronic administration of SOLIRIS resulted in a rapid and sustained reduction in complement-mediated thrombotic microangiopathy

Clinical efficacy and safety

Paroxysmal Nocturnal Haemoglobinuria (PNH)

The safety and efficacy of SOLIRIS in PNH patients with haemolysis were assessed in a randomized, double-blind, placebo-controlled 26-week study (C04-001). PNH patients were also treated with SOLIRIS in a single arm 52-week study (C04-002); and in a long-term extension study (E05-001). Patients received meningococcal vaccination prior to receipt of SOLIRIS. In all studies, the dose of eculizumab was 600 mg every 7 ± 2 days for 4 weeks, followed by 900 mg 7 ± 2 days later, then 900 mg every 14 ± 2 days for the study duration. Eculizumab was administered as an intravenous infusion over 25 – 45 minutes. An observational non-interventional Registry in patients with PNH (M07-001) was also initiated to characterize the natural history of PNH in untreated patients and the clinical outcomes during SOLIRIS treatment.

In study C04-001 (TRIUMPH) PNH patients with at least 4 transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH cells and platelet counts of at least 100,000/microliter were randomized to either SOLIRIS (n = 43) or placebo (n = 44). Prior to randomization, all patients underwent an initial observation period to confirm the need for RBC transfusion and to identify the haemoglobin concentration (the "set-point") which would define each patient's haemoglobin stabilization and transfusion outcomes. The haemoglobin set-point was less than or equal to 9 g/dL in patients with symptoms and was less than or equal to 7 g/dL in patients without symptoms. Primary efficacy endpoints were haemoglobin stabilization (patients who maintained a haemoglobin concentration above the haemoglobin set-point and avoid any RBC transfusion for the entire 26 week period) and blood transfusion requirement. Fatigue and health-related quality of life were relevant secondary endpoints. Haemolysis was monitored mainly by the measurement of serum LDH levels, and the proportion of PNH RBCs was monitored by flow cytometry. Patients receiving anticoagulants and systemic corticosteroids at baseline continued these medications. Major baseline characteristics were balanced (see Table 2).

In the non-controlled study C04-002 (SHEPHERD), PNH patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/microliter received SOLIRIS over a 52-week period. Concomitant medications included anti-thrombotic agents in 63% of the patients and systemic corticosteroids in 40% of the patients. Baseline characteristics are shown in Table 2.

Table 2: Patient Demographics and Characteristics in C04-001 and C04-002

	C04-001		**C04-002**
Parameter	**Placebo** N = 44	**SOLIRIS** N = 43	**SOLIRIS** N = 97
Mean Age (SD)	38.4 (13.4)	42.1 (15.5)	41.1 (14.4)
Gender - Female (%)	29 (65.9)	23 (53.5)	49 (50.5)
History of Aplastic Anemia or MDS (%)	12 (27.3)	8 (18.7)	29 (29.9)
Concomitant Anticoagulants (%)	20 (45.5)	24 (55.8)	59 (61)
Concomitant	16 (36.4)	14 (32.6)	46 (47.4)

Parameter	C04-001		C04-002
	Placebo N = 44	**SOLIRIS** N = 43	**SOLIRIS** N = 97
Steroids/Immunosuppressant Treatments (%)			
Discontinued treatment	10	2	1
PRBC in previous 12 months (median (Q1, Q3))	17.0 (13.5, 25.0)	18.0 (12.0, 24.0)	8.0 (4.0, 24.0)[4]
Mean Hgb level (g/dL) at setpoint (SD)	7.7 (0.75)	7.8 (0.79)	N/A
Pre-treatment LDH levels (median, U/L)	2,234.5	2,032.0	2,051.0
Free Haemoglobin at baseline (median, mg/dL)	46.2	40.5	34.9

In TRIUMPH, study patients treated with SOLIRIS had significantly reduced ($p< 0.001$) haemolysis resulting in improvements in anaemia as indicated by increased haemoglobin stabilization and reduced need for RBC transfusions compared to placebo treated patients (see Table 3). These effects were seen among patients within each of the three pre-study RBC transfusion strata (4 - 14 units; 15 - 25 units; > 25 units). After 3 weeks of SOLIRIS treatment, patients reported less fatigue and improved health-related quality of life. Because of the study sample size and duration, the effects of SOLIRIS on thrombotic events could not be determined. In SHEPHERD study, 96 of the 97 enrolled patients completed the study (one patient died following a thrombotic event). A reduction in intravascular haemolysis as measured by serum LDH levels was sustained for the treatment period and resulted in increased transfusion avoidance, a reduced need for RBC transfusion and less fatigue. See Table 3.

Table 3: Efficacy Outcomes in C04-001 and C04-002

	C04-001			C04-002*	
	Placebo N = 44	**SOLIRIS** N = 43	**P – Value**	**SOLIRIS** N = 97	**P – Value**
Percentage of patients with stabilized Hemoglobin levels at end of study	0	49	< 0.001	N/A	
PRBC transfused during treatment (median)	10	0	< 0.001	0	< 0.001
Transfusion Avoidance during treatment (%)	0	51	< 0.001	51	< 0.001
LDH levels at end of study (median, U/L)	2,167	239	< 0.001	269	< 0.001
LDH AUC at end of study (median, U/L x Day)	411,822	58,587	< 0.001	-632,264	< 0.001
Free Hemoglobin at end of study (median, mg/dL)	62	5	< 0.001	5	< 0.001

	C04-001			C04-002*	
	Placebo N = 44	**SOLIRIS** N = 43	**P – Value**	**SOLIRIS** N = 97	**P – Value**
FACIT-Fatigue (effect size)		1.12	< 0.001	1.14	< 0.001

* Results from study C04-002 refer to pre- versus post-treatment comparisons.

From the 195 patients that originated in C04-001, C04-002 and other initial studies, SOLIRIS-treated PNH patients were enrolled in a long-term extension study (E05-001). All patients sustained a reduction in intravascular haemolysis over a total SOLIRIS exposure time ranging from 10 to 54 months. There were fewer thrombotic events with SOLIRIS treatment than during the same period of time prior to treatment. However, this finding was shown in non-controlled clinical trials.

The PNH registry (M07-001) was used to evaluate the efficacy of SOLIRIS in PNH patients with no history of RBC transfusion. These patients had high disease activity as defined by elevated haemolysis (LDH ≥1.5x ULN) and the presence of related clinical symptom(s): fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin <100 g/L), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction.

In the PNH Registry, patients treated with SOLIRIS were observed to have a reduction in haemolysis and associated symptoms. At 6 months, patients treated with SOLIRIS with no history of RBC transfusion had significantly ($p<0.001$) reduced LDH levels (median LDH of 305 U/L; Table 4). Furthermore, 74% of the patients treated with SOLIRIS experienced clinically meaningful improvements in FACIT-Fatigue score (i.e., increase by 4 points or more) and 84% in EORTC fatigue score (i.e., decrease by 10 points or more).

Table 4: Efficacy Outcomes (LDH level and FACIT-Fatigue) in Patients with PNH with No History of Transfusion in M07-001

	M07-001
Parameter	**SOLIRIS** **No transfusion**
LDH level at baseline (median, U/L)	N=43 1447
LDH level at 6 months (median, U/L)	N=36 305
FACIT-Fatigue score at baseline (median)	N=25 32
FACIT-Fatigue score at last available assessment (median)	N=31 44

FACIT-Fatigue is measured on a scale of 0-52, with higher values indicating less fatigue

Atypical Haemolytic Uraemic Syndrome (aHUS)

Data from 100 patients in four prospective controlled studies, three in adult and adolescent patients (C08-002A/B C08-003A/B, C10-004) one in paediatric and adolescent patients

(C10-003) and 30 patients in one retrospective study (C09-001r) were used to evaluate the efficacy of SOLIRIS in the treatment of aHUS.

Study C08-002A/B was a prospective, controlled, open-label study which accrued patients in the early phase of aHUS with evidence of clinical thrombotic microangiopathy manifestations with platelet count ≤ 150 x 10^9/L despite PE/PI, and LDH and serum creatinine above upper limits of normal.

Study C08-003A/B was a prospective, single arm, open-label study which accrued patients with longer term aHUS without apparent evidence of clinical thrombotic microangiopathy manifestations and receiving chronic PE/PI (≥ 1 PE/PI treatment every two weeks and no more than 3 PE/PI treatments/week for at least 8 weeks before the first dose). Patients in both prospective studies were treated with SOLIRIS for 26 weeks and most patients enrolled into a long-term, open-label extension study. All patients enrolled in both prospective studies had an ADAMTS-13 level above 5%.

Patients received meningococcal vaccination prior to receipt of SOLIRIS or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. In all studies, the dose of SOLIRIS in adult and adolescent aHUS patients was 900 mg every 7 ± 2 days for 4 weeks, followed by 1,200 mg 7 ± 2 days later, then 1,200 mg every 14 ± 2 days for the study duration. SOLIRIS was administered as an intravenous infusion over 35 minutes. The dosing regimen in paediatric patients and adolescents weighing less than 40 kg was defined based on a pharmacokinetic (PK) simulation that identified the recommended dose and schedule based on body weight (see section 4.2).

Primary endpoints included platelet count change from baseline in Study C08-002A/B and thrombotic microangiopathy (TMA) event-free status in Study C08-003A/B. Additional endpoints included TMA intervention rate, haematologic normalization, complete TMA response, changes in LDH, renal function and quality of life. TMA-event free status was defined as the absence for at least 12 weeks of the following: decrease in platelet count of > 25% from baseline, PE/PI, and new dialysis. TMA interventions were defined as PE/PI or new dialysis. Haematologic normalization was defined as normalization of platelet counts and LDH levels sustained for ≥ 2 consecutive measurements for ≥ 4 weeks. Complete TMA response was defined as haematologic normalization and a ≥ 25% reduction in serum creatinine sustained in ≥ 2 consecutive measurements for ≥ 4 weeks.

Baseline characteristics are show in Table 5.

Table 5: Patient Demographics and Characteristics in C08-002A/B, and C08-003A/B

Parameter	**C08-002A/B**	**C08-003A/B**
	SOLIRIS N = 17	**SOLIRIS** N = 20
Time from first diagnosis until screening in months, median (min, max)	10 (0.26, 236)	48 (0.66, 286)
Time from current clinical TMA manifestation until screening in months, median (min, max)	<1 (<1, 4)	9 (1, 45)
Number of PE/PI sessions for current clinical TMA manifestation, median (min, max)	17 (2, 37)	62 (20, 230)

Parameter	C08-002A/B	C08-003A/B
	SOLIRIS N = 17	**SOLIRIS** N = 20
Number of PE/PI sessions in 7 days prior to first dose of eculizumab, median (min, max)	6 (0, 7)	2 (1, 3)
Baseline platelet count ($\times 10^9$/L), mean (SD)	109 (32)	228 (78)
Baseline LDH (U/L), mean (SD)	323 (138)	223 (70)
Patients without identified mutation, n (%)	4 (24)	6 (30)

Patients in aHUS Study C08-002A/B received SOLIRIS for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients continued to receive SOLIRIS by enrolling into an extension study. In aHUS Study C08-002A/B, the median duration of SOLIRIS therapy was approximately100 weeks (range: 2 weeks to 145 weeks).

A reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of SOLIRIS. Reduction in terminal complement activity was observed in all patients after commencement of SOLIRIS. Table 6 summarizes the efficacy results for aHUS Study C08-002A/B. All rates of efficacy endpoints improved or were maintained through 2 years of treatment. Complete TMA response was maintained by all responders. When treatment was continued for more than 26 weeks, two additional patients achieved and maintained Complete TMA response due to normalization of LDH (1 patient) and a decrease in serum creatinine (2 patients). Renal function, as measured by eGFR, was improved and maintained during SOLIRIS treatment. Four of the five patients who required dialysis at study entry were able to discontinue dialysis for the duration of SOLIRIS treatment, and one patient developed a new dialysis requirement. Patients reported improved health-related quality of life (QoL).

In aHUS Study C08-002A/B, responses to SOLIRIS were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

Patients in aHUS Study C08-003A/B received SOLIRIS for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients continued to receive SOLIRIS by enrolling into an extension study. In aHUS Study C08-003A/B, the median duration of SOLIRIS therapy was approximately 114 weeks (range: 26 to 129 weeks). Table 6 summarizes the efficacy results for aHUS Study C08-003A/B.

In aHUS Study C08-003A/B, responses to SOLIRIS were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins. Reduction in terminal complement activity was observed in all patients after commencement of SOLIRIS. All rates of efficacy endpoints improved or were maintained through 2 years of treatment. Complete TMA response was maintained by all responders. When treatment was continued for more than 26 weeks, six additional patients achieved and maintained Complete TMA response due to a decrease in serum creatinine. No patients required new dialysis with SOLIRIS. Renal function, as measured by median eGFR, increased during SOLIRIS therapy.

Table 6: Efficacy Outcomes in Prospective aHUS Studies C08-002A/B and C08-003A/B

	C08-002A/B N=17		**C08-003A/B N=20**	
	At 26 weeks	At 2 years[1]	At 26 weeks	At 2 years[1]
Normalization of platelet count All patients, n (%) (95% CI) Patients with abnormal baseline, n/n (%)	14 (82) (57-96) 13/15 (87)	15 (88) (64-99) 13/15 (87)	18 (90) (68-99) 1/3 (33)	18 (90) (68-99) 1/3 (33)
TMA event-free status, n (%) (95% CI)	15 (88) (64-99)	15 (88) (64-99)	16 (80) (56-94)	19 (95) (75-99)
TMA intervention rate Daily pre-eculizumab rate, median (min, max) Daily during-eculizumab rate, median (min, max) *P*-value	0.88 (0.04, 1.59) 0 (0, 0.31) *P*<0.0001	0.88 (0.04, 1.59) 0 (0, 0.31) *P*<0.0001	0.23 (0.05, 1.09) 0 *P* <0.0001	0.23 (0.05, 1.09) 0 *P*<0.0001
CKD improvement by ≥1 stage, n (%) (95% CI)	10 (59) (33-82)	12 (71) (44-90)	7 (35) (15-59)	12 (60) (36-81)
eGFR change ml/min/1.73 m^2: median (range)	20 (-1, 98)	28 (3, 82)	5 (-1, 20)	11 (-42, 30)
eGFR improvement ≥15 ml/min/1.73 m^2, n (%) (95% CI)	8 (47) (23-72)	10 (59) (33-82)	1 (5) (0-25)	8 (40) (19-64)
Change in Hgb > 20g/L, n (%) (95% CI)	11 (65) (38-86) [2]	13 (76) (50-93)	9 (45) (23-68) [3]	13 (65) (41-85)
Haematologic normalization, n (%) (95% CI)	13 (76) (50-93)	15 (88) (64-99)	18 (90) (68-99)	18 (90) (68-99)
Complete TMA response, n (%) (95% CI)	11(65) (38-86)	13(76) (50-93)	5 (25) (9-49)	11(55) (32-77)

[1] At data cut off (20 April 2012)
[2] Study C08-002: 3 patients received ESA which was discontinued after eculizumab initiation
[3] Study C08-003: 8 patients received ESA which was discontinued in 3 of them during eculizumab therapy

aHUS Study C10-004 enrolled 41 patients who displayed signs of thrombotic microangiopathy (TMA). In order to qualify for enrolment, patients were required to have a platelet count < lower limit of normal range (LLN), evidence of haemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the

need for chronic dialysis. The median patient age was 35 (range: 18 to 80 years). All patients enrolled in aHUS Study C10-004 had an ADAMTS-13 level above 5%. Fifty-one percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 35 patients received PE/PI prior to eculizumab. Table 7 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in aHUS C10-004.

Table 7: Baseline Characteristics of Patients Enrolled in aHUS Study C10-004

Parameter	**aHUS Study C10-004** N = 41
Time from aHUS diagnosis to first study dose (months), median (min, max)	0.79 (0.03, 311)
Time from current clinical TMA manifestation until first study dose (months), median (min, max)	0.52 (0.03, 19)
Baseline platelet count ($\times 10^9$/L), median (min, max)	125 (16, 332)
Baseline LDH (U/L), median (min, max)	375 (131, 3318)
Baseline eGFR (ml/min/1.73m^2), median (min, max)	10 (6, 53)

Patients in aHUS Study C10-004 received SOLIRIS for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients elected to continue on chronic dosing.

Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of SOLIRIS. SOLIRIS reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In aHUS C10-004, mean (±SD) platelet count increased from 119 ± 66 x10^9/L at baseline to 200 ± 84 x10^9/L by one week; this effect was maintained through 26 weeks (mean platelet count (±SD) at week 26: 252 ± 70 x10^9/L). Renal function, as measured by eGFR, was improved during SOLIRIS therapy. Twenty of the 24 patients who required dialysis at baseline were able to discontinue dialysis during SOLIRIS treatment. Table 8 summarizes the efficacy results for aHUS study C10-004.

Table 8: Efficacy Outcomes in Prospective aHUS Study C10-004

Efficacy Parameter	**aHUS Study C10-004** **(N = 41)** At 26-weeks
Change in platelet count through week 26 (10^9/L)	111 (-122, 362)
Hematologic Normalization, n (%) Median duration of hematologic normalization, weeks (range) [1]	36 (88) 46 (10, 74)
Complete TMA response, n (%) Median duration of complete TMA response, weeks (range) [1]	23 (56) 42 (6, 74)
TMA Event-free Status, n (%) 95% CI	37 (90) 77; 97

Efficacy Parameter	aHUS Study C10-004 (N = 41) At 26-weeks
Daily TMA Intervention Rate, median (range) Before eculizumab On eculizumab treatment	 0.63 (0, 1.38) 0 (0, 0.58)

[1] Through data cut-off (September 4, 2012), with median duration of SOLIRIS therapy of 50 weeks (range: 13 weeks to 86 weeks).

Longer term treatment with SOLIRIS (median 52 weeks ranging from 15 to 126 weeks) was associated with an increased rate of clinically meaningful improvements in adult patients with aHUS. When SOLIRIS treatment was continued for more than 26 weeks, three additional patients (63% of patients in total) achieved Complete TMA response and four additional patients (98% of patients in total) achieved hematologic normalization. At the last evaluation, 25 of 41 patients (61%) achieved eGFR improvement of ≥ 15 ml/min/1.73 m^2 from baseline.

Paediatric Population

Paroxysmal Nocturnal Haemoglobinuria

A total of 7 PNH paediatric patients, with a median weight of 57.2 kg (range of 48.6 to 69.8 kg) and aged from 11 to 17 years (median age: 15.6 years), received SOLIRIS in study M07-005.

Treatment with eculizumab at the proposed dosing regimen in the paediatric population was associated with a reduction of intravascular haemolysis as measured by serum LDH level. It also resulted in a marked decrease or elimination of blood transfusions, and a trend towards an overall improvement in general function. The efficacy of eculizumab treatment in paediatric PNH patients appears to be consistent with that observed in adult PNH patients enrolled in PNH pivotal Studies (C04-001 and C04-002) (Table 3 and 9).

Table 9: Efficacy Outcomes in Paediatric PNH Study M07-005

		P – Value	
	Mean (SD)	Wilcoxon Signed Rank	Paired t-test
Change from baseline at 12 weeks of LDH Value (U/L)	-771 (914)	0.0156	0.0336
LDH AUC (U/L x Day)	-60,634 (72,916)	0.0156	0.0350
Change from baseline at 12 weeks in Plasma Free Haemoglobin (mg/dL)	-10.3 (21.13)	0.2188	0.1232
Change from baseline Type III RBC clone size (Percent of aberrant cells)	1.80 (358.1)		
Change from baseline at 12 weeks of PedsQL™4.0 Generic Core scale (patients)	10.5 (6.66)	0.1250	0.0256
Change from baseline at 12 weeks of PedsQL™4.0 Generic Core scale	11.3 (8.5)	0.2500	0.0737

		P – Value	
	Mean (SD)	Wilcoxon Signed Rank	Paired t-test
(parents)			
Change from baseline at 12 weeks of PedsQL™ Multidimensional Fatigue (patients)	0.8 (21.39)	0.6250	0.4687
Change from baseline at 12 weeks of PedsQL™ Multidimensional Fatigue (parents)	5.5 (0.71)	0.5000	0.0289

Atypical Haemolytic Uremic Syndrome

A total of 15 paediatric patients (ages 2 months to 12 years) received SOLIRIS in aHUS Study C09-001r. Forty seven percent of patients had an identified complement regulatory factor mutation or auto-antibody. The median time from aHUS diagnosis to first dose of SOLIRIS was 14 months (range < 1 to 110 months). The median time from current thrombotic microangiopathy manifestation to first dose of SOLIRIS was 1 month (range < 1 to 16 months). The median duration of SOLIRIS therapy was 16 weeks (range 4 to 70 weeks) for children under 2 years of age (n = 5) and 31 weeks (range 19 to 63 weeks) for children 2 years to less than 12 years of age (n = 10).

Overall, the efficacy results of these paediatric patients appeared consistent with what was observed in patients enrolled in aHUS pivotal Studies C08-002 and C08-003 (Table 6). No paediatric patient required new dialysis during treatment with SOLIRIS.

Table 10: Efficacy Results in Paediatric Patients Enrolled in aHUS C09-001r

Efficacy Parameter	<2 years (n=5)	2 to <12 years (n=10)	<12 years (n=15)
Patients with platelet count normalization, n (%)	4 (80)	10 (100)	14 (93)
Complete TMA response, n (%)	2 (40)	5 (50)	7 (50)
Daily TMA intervention rate, median (range)			
Before eculizumab	1 (0, 2)	<1 (0.07, 1.46)	<1 (0, 2)
On eculizumab treatment	<1 (0, <1)	0 (0, <1)	0 (0, <1)
Patients with eGFR improvement ≥15 ml/min/1.73 m^2, n (%)	2 (40)	6 (60)	8 (53)

In paediatric patients with shorter duration of current severe clinical thrombotic microangiopathy (TMA) manifestation prior to eculizumab, there was TMA control and improvement of renal function with eculizumab treatment (Table 10).

In paediatric patients with longer duration of current severe clinical TMA manifestation prior to eculizumab, there was TMA control with eculizumab treatment. However, renal function was not changed due to prior irreversible kidney damage (Table 11).

Table 11: Efficacy Outcomes in Paediatric Patients in Study C09-001r according to duration of current severe clinical thrombotic microangiopathy (TMA) manifestation

	Duration of current severe clinical TMA manifestation	
	< 2 months N=10 (%)	**>2 months N=5 (%)**
Platelet count normalization	9 (90)	5 (100)
TMA event-free status	8 (80)	3 (60)
Complete TMA response	7 (70)	0
eGFR improvement ≥ 15 ml/min/1.73m^2	7 (70)	0*

*One patient achieved eGFR improvement after renal transplant

A total of 22 paediatric and adolescents patients (aged 5 months to 17 years) received SOLIRIS in aHUS Study C10-003.

In Study C10-003, patients who enrolled in the study were required to have a platelet count < lower limit of normal range (LLN), evidence of haemolysis such as an elevation in serum LDH above the upper limits of normal and serum creatinine level ≥97 percentile for age without the need for chronic dialysis. The median patient age was 6.5 years (range: 5 months to 17 years). Patients enrolled in aHUS C10-003 had an ADAMTS-13 level above 5%. Fifty percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 10 patients received PE/PI prior to eculizumab. Table 12 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in aHUS Study C10-003.

Table 12: Baseline Characteristics of Paediatric and Adolescents Patients Enrolled in aHUS Study C10-003

Parameter	**1 month to <12 years (N = 18)**	**All Patients (N = 22)**
Time from aHUS diagnosis until first study dose (months) median (min, max)	0.51 (0.03, 58)	0.56 (0.03,191)
Time from current clinical TMA manifestation until first study dose (months), median (min, max)	0.23 (0.03, 4)	0.20 (0.03, 4)
Baseline platelet count (x 10^9/L), median (min, max)	110 (19, 146)	91 (19,146)
Baseline LDH (U/L) median (min, max)	1510 (282, 7164)	1244 (282, 7164)
Baseline eGFR (ml/min/1.73 m^2), median (min, max)	22 (10, 105)	22 (10, 105)

Patients in aHUS C10-003 received SOLIRIS for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients elected to continue on chronic dosing. Reduction in terminal complement activity was observed in all patients after commencement of SOLIRIS. SOLIRIS reduced signs of complement-mediated TMA activity, as shown by an

increase in mean platelet counts from baseline to 26 weeks. The mean (±SD) platelet count increased from 88 ± 42 $x10^9$/L at baseline to 281 ± 123 $x10^9$/L by one week; this effect was maintained through 26 weeks (mean platelet count (±SD) at week 26: 293 ± 106 $x10^9$/L). Renal function, as measured by eGFR, was improved during SOLIRIS therapy. Nine of the 11 patients who required dialysis at baseline no longer required dialysis after Study Day 15 of eculizumab treatment. Responses were similar across all ages from 5 months to 17 years of age. In aHUS C10-003, responses to SOLIRIS were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

Table 13 summarizes the efficacy results for aHUS C10-003.

Table 13: Efficacy Outcomes in Prospective aHUS Study C10-003

Efficacy Parameter	**1 month to <12 years (N = 18) At 26-weeks**	**All Patients (N = 22) At 26-weeks**
Complete Hematologic Normalization, n (%) Median Duration of complete hematologic normalization, weeks (range) [1]	14 (78) 35 (13, 78)	18 (82) 35 (13, 78)
Complete TMA response, n (%) Median Duration of complete TMA response, weeks (range)[1]	11 (61) 40 (13, 78)	14 (64) 37 (13, 78)
TMA Event-Free Status, n (%) 95% CI	17 (94) NA	21 (96) 77; 99
Daily TMA Intervention rate, median (range) Before eculizumab treatment, median On eculizumab treatment, median	 NA NA	0.4 (0, 1.7) 0 (0, 1.01)
eGFR improvement ≥15 ml/min/ 1.73•m^2, n (%)	16 (89)	19 (86)
Change in eGFR (≥15 ml/min/1.73•m^2) at 26 weeks, median (range)	64 (0,146)	58 (0, 146)
CKD improvement by ≥1 stage, n (%)	14/16 (88)	17/20 (85)
PE/PI Event-Free Status, n (%) New Dialysis Event-Free Status, n (%) 95% CI	16 (89) 18 (100) NA	20 (91) 22 (100) 85;100

[1] Through data cut-off (October 12, 2012), with median duration of SOLIRIS therapy of 44 weeks (range: 1dose to 88 weeks).

Longer term treatment with SOLIRIS (median 55 weeks ranging from 1day to 107 weeks) was associated with an increased rate of clinically meaningful improvements in paediatric and adolescent patients with aHUS. When SOLIRIS treatment was continued for more than 26 weeks, one additional patient (68% of patients in total) achieved Complete TMA Response and two additional patients (91% of patients in total) achieved hematologic normalization. At the last evaluation, 19 of 22 patients (86%) achieved eGFR improvement of $\geqslant$ 15 ml/min/1.73 m^2 from baseline. No patient required new dialysis with SOLIRIS.

5.2 Pharmacokinetic properties

Pharmacokinetics and Drug Metabolism

Biotransformation

Human antibodies undergo endocytotic digestion in the cells of the reticuloendothelial system. Eculizumab contains only naturally occurring amino acids and has no known active metabolites. Human antibodies are predominately catabolized by lysosomal enzymes to small peptides and amino acids.

Elimination

No specific studies have been performed to evaluate the hepatic, renal, lung, or gastrointestinal routes of excretion/elimination for SOLIRIS. In normal kidneys, antibodies are not excreted and are excluded from filtration by their size.

Pharmacokinetic Parameters

In 40 patients with PNH, a 1-compartmental model was used to estimate pharmacokinetic parameters after multiple doses. Mean clearance was 0.31 ± 0.12 ml/hr/kg, mean volume of distribution was 110.3 ± 17.9 ml/kg, and mean elimination half-life was 11.3 ± 3.4 days. Based on these data, the onset of steady state is predicted to be approximately 49 – 56 days.

In PNH patients, pharmacodynamic activity correlates directly with eculizumab serum concentrations and maintenance of trough levels above ≥ 35 microgram/ml results in essentially complete blockade of haemolytic activity in the majority of PNH patients.

A second population PK analysis with a standard 1 compartmental model was conducted on the multiple dose PK data from 37 aHUS patients receiving the recommended SOLIRIS regimen in studies C08-002A/B and C08-003A/B. In this model, the clearance of SOLIRIS for a typical aHUS patient weighing 70 kg was 0.0139 L/hr and the volume of distribution was 5.6 L. The elimination half-life was 297 h (approximately 12.4 days).

The second population PK model was applied to the multiple dose PK data from 22 paediatric aHUS patients receiving the recommended SOLIRIS regimen in aHUS C10-003. The clearance and volume of distribution of SOLIRIS are weight dependent, which forms the basis for a weight categorical based dose regimen in paediatric patients (see section 4.2). Clearance values of SOLIRIS in paediatric aHUS patients were 10.4, 5.3, and 2.2 ml/hr with body weight of 70, 30, and 10 kg, respectively; and the corresponding volume of distribution values were 5.23, 2.76, and 1.21 L, respectively. The corresponding elimination half-life remained almost unchanged within a range of 349 to 378 h (approximately 14.5 to 15.8 days).

The clearance and half-life of eculizumab were also evaluated during plasma exchange interventions. Plasma exchange resulted in an approximately 50% decline in eculizumab concentrations following a 1-hour intervention and the elimination half-life of eculizumab was reduced to 1.3 hours. Supplemental dosing is recommended when SOLIRIS is administered to aHUS patients receiving plasma infusion or exchange (see section 4.2).

All aHUS patients treated with SOLIRIS when administered as recommended demonstrated rapid and sustained reduction in terminal complement activity. In aHUS patients, pharmacodynamic activity correlates directly with eculizumab serum concentrations and

maintenance of trough levels of approximately 50-100 microgram/ml result in essentially complete blockade of terminal complement activity in all aHUS patients.

Special Populations

PNH

Dedicated studies have not been conducted to evaluate the pharmacokinetics of SOLIRIS administration in special PNH patient populations identified by gender, race, age (geriatric), or the presence of renal or hepatic impairment.

Paediatric population

The pharmacokinetics of eculizumab was evaluated in Study M07-005 including 7 PNH paediatric patients (aged from 11 to less than 18 years).

Weight was a significant covariate resulting in a lower eculizumab clearance 0.0105 L/h in the adolescent patients. Dosing for paediatric patients <40 kg is based on paediatric patients with aHUS.

aHUS

The pharmacokinetics of SOLIRIS have been studied in aHUS patients with a range of renal impairment and age. There have been no observed differences in PK parameters noted in these subpopulations of aHUS patients.

5.3 Preclinical safety data

The specificity of eculizumab for C5 in human serum was evaluated in two *in vitro* studies.

The tissue cross-reactivity of eculizumab was evaluated by assessing binding to a panel of 38 human tissues. C5 expression in the human tissue panel examined in this study is consistent with published reports of C5 expression, as C5 has been reported in smooth muscle, striated muscle, and renal proximal tubular epithelium. No unexpected tissue cross-reactivity was observed.

Animal reproduction studies have not been conducted with eculizumab due to lack of pharmacologic activity in non-human species.

In a 26-week toxicity study performed in mice with a surrogate antibody directed against murine C5, treatment did not affect any of the toxicity parameters examined. Haemolytic activity during the course of the study was effectively blocked in both female and male mice.

No clear treatment-related effects or adverse effects were observed in reproductive toxicology studies in mice with a surrogate terminal complement inhibitory antibody, which was utilized to assess the reproductive safety of C5 blockade. These studies included assessment of fertility and early embryonic development, developmental toxicity, and pre- and post-natal development.

When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose (approximately 4 times the maximum recommended human SOLIRIS dose, based on a body weight comparison); however, the exposure did not increase foetal loss or neonatal death.

No animal studies have been conducted to evaluate the genotoxic and carcinogenic potential of eculizumab or its effect on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate, monobasic
Sodium phosphate, dibasic
Sodium chloride
Polysorbate 80
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

30 months.

After dilution, the medicinal product should be used immediately. However, chemical and physical stability has been demonstrated for 24 hours at 2°C – 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8ºC).
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.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

30 ml of concentrate in a vial (Type I glass) with a stopper (butyl, siliconised), and a seal (aluminium) with flip-off cap (polypropylene).

Pack size of one vial.

6.6 Special precautions for disposal and other handling

Prior to administration, the SOLIRIS solution should be visually inspected for particulate matter and discolouration.

Instructions:

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

Withdraw the total amount of SOLIRIS from the vial(s) using a sterile syringe.

Transfer the recommended dose to an infusion bag.

Dilute SOLIRIS to a final concentration of 5 mg/ml by addition to the infusion bag using sodium chloride 9mg/ml (0.9%) solution for injection, sodium chloride 4.5mg/ml (0.45%) solution for injection, or 5% Dextrose in water, as the diluent.

The final volume of a 5 mg/ml diluted solution is 60 ml for 300 mg doses, 120 ml for 600 mg doses, 180 ml for 900 mg doses and 240 ml for 1,200 mg doses. The solution should be clear and colourless.

Gently agitate the infusion bag containing the diluted solution to ensure thorough mixing of the product and diluent.

The diluted solution should be allowed to warm to room temperature prior to administration by exposure to ambient air.

Discard any unused portion left in a vial, as the product contains no preservatives.

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

Product Owner

Alexion Pharmaceuticals International Operations Limited
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