AUSTRALIAN PRODUCT INFORMATION

SOLIRIS® (ECULIZUMAB *RMC)*

CONCENTRATED SOLUTION FOR INTRAVENOUS INFUSION

WARNING: SERIOUS MENINGOCOCCAL INFECTION
SOLIRIS increases the risk of meningococcal infections

- **Life-threatening meningococcal infections/sepsis have occurred in patients treated with SOLIRIS. Meningococcal infection may become rapidly life-threatening or fatal if not recognised and treated early (see section 4.4 Special Warnings and Precautions for Use).**
- **Vaccinate patients against meningococcal infection (*Neisseria meningitidis*), at least 2 weeks prior to receiving SOLIRIS, unless the risk of delaying SOLIRIS therapy outweighs the risk of meningococcal infection.**
- **Vaccinate and/or revaccinate according to current national vaccination guidelines such as the Australian Immunisation Handbook; vaccines against serogroups A, B, C, Y and W135 are recommended.**
- **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.**
- **Monitor patients for early signs of meningococcal infections, evaluate immediately if infection is suspected, and treat with antibiotics if necessary.**

1 NAME OF THE MEDICINE

Eculizumab *rmc*

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SOLIRIS is supplied as 300 mg single-use glass vials containing 30 mL of 10 mg/mL sterile, preservative-free SOLIRIS solution per vial.

Excipients with known effect: sodium chloride (5 mmol per vial)

For the full list of excipients, see *section 6.1 - List of excipients*.

3 PHARMACEUTICAL FORM

SOLIRIS (eculizumab *rmc)* concentrated solution for intravenous infusion is a sterile, clear, colourless, preservative-free solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SOLIRIS is indicated for the treatment of patients with:

- Paroxysmal Nocturnal Haemoglobinuria (PNH) to reduce haemolysis.
- atypical Haemolytic Uraemic Syndrome (aHUS).
- Adult patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive.

  SOLIRIS is not intended for acute treatment of a NMOSD relapse.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Patients must be administered a meningococcal vaccine at least two weeks prior to receiving SOLIRIS therapy. Refer to Box Warning and *section 4.4 – Special Warnings and Precautions for Use; Meningococcal Infection* and *Immunisation*, for vaccination information before initiating SOLIRIS treatment.

SOLIRIS should be administered by a healthcare professional and under appropriate medical supervision.

Adult Patients (≥18 years of age)

Paroxysmal Nocturnal Haemoglobinuria (PNH)

The PNH dosing regimen for adult patients 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 on the fifth week, followed by 900 mg of SOLIRIS administered via a 25 - 45 minute intravenous infusion every 14 ± 2 days.

atypical Haemolytic Uraemic Syndrome (aHUS) and Neuromyelitis Optica Spectrum Disorder (NMOSD)

The aHUS and NMOSD dosing regimen for adult patients consists of a 4-week initial phase followed by a maintenance phase:

- Initial phase: 900 mg of SOLIRIS via a 25 - 45 minute intravenous infusion every week for the first 4 weeks
- Maintenance phase: 1200 mg of SOLIRIS administered via a 25 - 45 minute intravenous infusion on the fifth week, followed by 1200 mg of SOLIRIS administered via a 25 - 45 minute intravenous infusion every 14 ± 2 days.

For patients with NMOSD, SOLIRIS should be administered as an adjuvant therapy to their existing immunosuppressive therapy (IST). In clinical studies with SOLIRIS, ~76% of patients were on ISTs at baseline (refer to section 5.1 Pharmacodynamic Properties; Clinical Trials).

Refer to section 4.4 – Special Warnings and Precautions for Use; Immunosuppressant Therapy (IST) for ISTs that are not to be used along with SOLIRIS.

Paediatric Patients (<18 years of age)

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

For paediatric patients with PNH and aHUS with a body weight below 40 kg, the SOLIRIS dosing regimen is presented in Table 1.

Table 1: **SOLIRIS weight-based Dosage Regimen in Paediatric Patients with PNH or aHUS**

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

* SOLIRIS has not been studied in patients with PNH who weigh < 40 kg. The dosing for patients with PNH < 40 kg weight is based on the dosing used for patients with aHUS and who weigh < 40 kg.

The safety and efficacy of SOLIRIS for the treatment of NMOSD in paediatric patients below the age of 18 years have not been established.

Treatment Monitoring/Dose Modifications

Patients with PNH may need to be monitored to see whether the 14 day dosing schedule needs to be reduced to 12 days (refer to section 4.4 – Special Warnings and Precautions for Use).

Patients with aHUS should be monitored for signs and symptoms of thrombotic microangiopathy (TMA) (refer to section 4.4 – Special Warnings and Precautions for Use).

SOLIRIS treatment is recommended to continue for the patient's lifetime, unless the discontinuation of SOLIRIS is clinically indicated.

SOLIRIS should be administered at the recommended dosage regimen time points, or within 2 days of these time points. If a patient misses a scheduled dose, monitor for signs and symptoms of a TMA complication (refer to section 4.4 – Special Warnings and Precautions for Use; Laboratory Monitoring) and resume the regular schedule as soon as possible. If a patient misses multiple doses of SOLIRIS re-induction can be considered.

Supplemental dosing of SOLIRIS is required in the setting of concomitant Plasma intervention (plasmapheresis [PP] or plasma exchange [PE], or plasma infusion [PI]) as described in Table 2.

Table 2: **Supplemental Dose of SOLIRIS with concomitant Plasma Intervention**

Type of Plasma Intervention	Most Recent SOLIRIS Dose	Supplemental SOLIRIS Dose With Each Plasma Intervention	Timing of Supplemental SOLIRIS Dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange session
	≥ 600 mg	600 mg per each plasmapheresis or plasma exchange session	
Plasma infusion	≥ 300 mg	300 mg per plasma infusion session	60 minutes prior to each plasma infusion session

Method of Administration

Preparation for Administration

SOLIRIS must be diluted to a final admixture concentration of 5 mg/mL using the following steps:

- Withdraw the total amount of SOLIRIS from the vial(s) into a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute SOLIRIS to a final concentration of 5 mg/mL by adding the appropriate amount (equal volume of diluent to SOLIRIS volume – refer to table 3 below) of 0.9% Sodium Chloride Injection USP; 0.45% Sodium Chloride Injection USP; 5% Dextrose in Water Injection USP; or Ringer's Solution for Intravenous Infusion USP to the infusion bag.
- Do not mix with other medicinal products.

Table 3: Preparation and Reconstitution of SOLIRIS

SOLIRIS Dose	Diluent Volume	Final Volume
300 mg	30 mL	60 mL
600 mg	60 mL	120 mL
900 mg	90 mL	180 mL
1200 mg	120 mL	240 mL

Product is for single use in one patient only. Discard any unused portion left in a vial, as the product contains no preservatives.

Gently invert the infusion bag containing the diluted SOLIRIS solution to ensure thorough mixing of the product and diluent. Prior to administration, the admixture should be allowed to reach 18° to 25°C. The admixture must not be heated in a microwave or with any heat source other than ambient air temperature. The SOLIRIS admixture should be inspected visually for particulate matter and discolouration prior to administration.

Do Not Administer as an Intravenous Push or Bolus Injection.

The SOLIRIS admixture should be administered by intravenous infusion over 25 to 45 minutes in adults, and 1 to 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.

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 2 hours in adults and 4 hours in paediatric patients. Monitor the patient for at least 1 hour following completion of the infusion for signs or symptoms of an infusion reaction.

Dosage Adjustment

Paediatric Population
The route of administration of SOLIRIS is the same for all age groups.

Renal Impairment
No dose adjustment is required for patients with renal impairment.

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 – List of excipients.

Do not initiate SOLIRIS therapy in 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).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Meningococcal Infections

Due to its mechanism of action, the use of SOLIRIS increases the patient's susceptibility to meningococcal infection (*Neisseria meningitidis*). Meningococcal infection 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 risk of 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, B, C, Y and W135 are recommended in minimising infection with the commonly pathogenic meningococcal serogroups (refer to section 4.4 – Special Warnings and Precautions for Use; Immunisation). Vaccinate and/or revaccinate according to the current national vaccination guidelines such as the Australian Immunisation Handbook.

For patients stabilised on SOLIRIS and receiving maintenance therapy, and for whom additional vaccination is warranted, careful consideration should be given to the timing

of vaccination relative to administration of SOLIRIS (refer to section 4.4 – Special Warnings and Precautions for Use; Immunisation).

Cases of serious or fatal meningococcal infections have been reported in SOLIRIS-treated patients. Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents. 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 (refer to section 4.4 – Special Warnings and Precautions for Use; Educational Materials).

Other Systemic Infections

Due to its mechanism of action, SOLIRIS therapy should be administered with caution to patients with active systemic infections. SOLIRIS blocks terminal complement activation; therefore patients may have increased susceptibility to infections, especially with *Neisseria* and encapsulated bacteria. Serious infections with *Neisseria* species (other than *N. meningitidis*), including disseminated gonococcal infections, have been reported.

Patients should be provided with information from the Patient/Parent Guide to increase their awareness of potential serious infections and their signs and symptoms. Counsel patients about gonorrhoea prevention and advise regular testing for patients at-risk.

Infusion Reactions

Administration of SOLIRIS may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis). Immune system disorders within 48 hours of SOLIRIS administration did not differ from placebo treatment in PNH, aHUS, NMOSD and other studies conducted with SOLIRIS. In clinical trials, no PNH, aHUS or NMOSD 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, low titre antibody responses have been detected in SOLIRIS -treated patients across all studies. In placebo-controlled studies in patients with PNH treated with SOLIRIS, low titre 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%) of patients with aHUS had low positive values for neutralising antibodies. In an NMOSD placebo-controlled study, 2/95 (2.1%) of the SOLIRIS-treated patients showed antidrug antibody (ADA) response. Positive ADA samples were low titre and transient. Both patients were negative for neutralising antibodies.

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

Immunisation

Patients under 18 years of age must be vaccinated against *Haemophilus influenzae* and S*treptococcus pneumoniae* and strictly adhere to the national vaccination recommendations of each age group.

All patients must be vaccinated against meningococcal infections (*Neisseria meningitidis*) at least 2 weeks prior to receiving SOLIRIS, unless the risk of delaying SOLIRIS therapy outweighs the risk of 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 (refer to section 4.4 – Special Warnings and Precautions for Use; Meningococcal Infection). Vaccines against serogroups A, B, C, Y and W135 are recommended in minimising infection with the commonly pathogenic meningococcal serogroups.

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

For patients stabilised on SOLIRIS and receiving maintenance therapy, and for whom additional vaccination is warranted, careful consideration should be given to the timing of vaccination (or booster in patients previously vaccinated against meningococcal infections) relative to administration of SOLIRIS.

Patients must be vaccinated or revaccinated according to current national vaccination guidelines such as the Australian Immunisation Handbook.

Anticoagulant Therapy

The effect of withdrawal of anticoagulant therapy during SOLIRIS treatment has not been established. Treatment with SOLIRIS should not alter anticoagulant management.

Immunosuppressant Therapy

The safety and efficacy of eculizumab, when administered as an adjuvant therapy along with rituximab and mitoxantrone has not been studied in patients with NMOSD, refer to section 5.1 Pharmacodynamic Properties, Clinical Trials.

Patients who entered NMOSD clinical trials while receiving background immunosuppressant therapy continued treatment with immunosuppressant therapy while on SOLIRIS treatment. Withdrawal of immunosuppressant therapy during SOLIRIS treatment for NMOSD was not assessed in the placebo-controlled study. If background immunosuppressant therapy is decreased or discontinued, patients should be monitored closely for signs and symptoms of potential NMOSD relapse.

Laboratory Monitoring

<u>PNH</u>

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

<u>aHUS</u>

Patients with aHUS receiving SOLIRIS should be monitored for thrombotic microangiopathy (TMA) 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).

Monitoring after SOLIRIS Discontinuation

Treatment Discontinuation for PNH

If patients with PNH discontinue treatment with SOLIRIS they should be closely 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 red blood cell 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

Severe thrombotic microangiopathy (TMA) complications were observed following SOLIRIS discontinuation in aHUS clinical studies (in some patients up to 127 weeks after discontinuation) and can occur at any time. Discontinuation of treatment is not recommended unless medically justified. Close monitoring of patients with aHUS who discontinue SOLIRIS treatment for signs and symptoms of severe TMA complications should commence immediately after discontinuation.

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.

Monitoring may be insufficient to predict or prevent severe TMA complications in patients with aHUS.

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.

Sixty one patients (21 paediatric) discontinued SOLIRIS in the aHUS clinical trials (median follow up 24 weeks). Fifteen severe TMA complications were observed in 12 patients following treatment discontinuation, and 2 severe TMA complications occurred in 2 additional patients that received a reduced SOLIRIS dose outside the approved dosing regimen. Severe TMA complications occurred regardless of whether the patient had an identified genetic mutation, high risk polymorphism or auto-antibodies.

Additional serious medical complications occurred in these patients, including severe worsening of kidney function, progression to end stage renal disease requiring dialysis and disease-related hospitalisation. Despite SOLIRIS re-initiation following discontinuation, progression to end stage renal disease occurred in 1 patient.

Treatment Discontinuation for NMOSD

Use of SOLIRIS in NMOSD treatment has been studied only in the setting of chronic administration and the effect of SOLIRIS discontinuation has not been characterised. Patients who discontinue SOLIRIS treatment should be carefully monitored for signs and symptoms of potential NMOSD relapse.

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 Guide and a Patient Safety Information 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.

Patients on Controlled Sodium Diets

SOLIRIS contains 5 mmol sodium per vial. This should be taken into consideration when calculating the sodium intake of patients on a controlled sodium diet.

Use in the Elderly

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

Paediatric Use

SOLIRIS has not been studied in PNH paediatric patients who weigh less than 40 kg, or in paediatric patients with NMOSD.

Effects on Laboratory Tests

There are no drug-laboratory interactions known at this time.

The efficacy and safety of SOLIRIS have not been established for the treatment of patients with Shiga and Shiga-like toxin (verocytotoxin-related haemolytic uraemic syndrome (so called classic HUS).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

PP, PE and PI have been shown to reduce SOLIRIS serum levels. A supplemental dose of SOLIRIS is required in these settings. Refer to section 4.2 Dose and Method of

Administration - Treatment Monitoring/Dose Modifications for guidance in case of concomitant PE, PP and PI treatment.

Concomitant use of SOLIRIS with neonatal Fc receptor (FcRn) blockers may lower systemic exposures and reduce effectiveness of SOLIRIS. Closely monitor for reduced effectiveness of SOLIRIS.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No studies have been conducted to assess the effects of eculizumab on male and female fertility. In animal studies with a surrogate terminal complement inhibitor (murine anti-C5) antibody, no adverse effects on the fertility of treated mice were observed.

Use in Pregnancy - Category B2

There are no well-controlled studies in pregnant women treated with SOLIRIS. Post-market data and literature on a limited number of pregnancies exposed to SOLIRIS (less than 300 pregnancy outcomes) indicate there is no increased risk of fetal malformation or fetal-neonatal toxicity compared to the existing risk in PNH and aHUS; however, due to the lack of well-controlled studies, uncertainties remain. As an IgG antibody, eculizumab is expected to cross the placenta. Animal studies conducted with a surrogate antibody did not reveal obvious teratogenicity, but are of limited predictive value. There is not enough data to determine the risks of SOLIRIS use during pregnancy. Use of SOLIRIS in pregnancy should be carefully considered, with regards to the specific risks (including maternal and neonatal death and non-live birth) and benefits for each patient. An individual risk benefit analysis is recommended before starting and during treatment with SOLIRIS in pregnant women. Should treatment be considered necessary during pregnancy, close maternal and fetal monitoring according to local guidelines is recommended.

SOLIRIS should be used during pregnancy only if the potential benefit justifies the potential risk to the mother, fetus and/or neonate. Unless pregnancy is specifically desired, women should use adequate contraception during SOLIRIS treatment, and for up to 5 months after discontinuing treatment.

Clinical Considerations

There are risks to the mother and fetus associated with treated and untreated PNH and aHUS. PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages and increased maternal mortality, and adverse fetal outcomes, including fetal death and premature delivery. aHUS in pregnancy is associated with adverse maternal outcomes, including pre-eclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including intrauterine growth restriction (IUGR), fetal death and low birth weight. There is a risk of maternal, fetal or neonatal death with both PNH and aHUS pregnancies whether treated with SOLIRIS or not.

Human Data

Limited data are available from reports of pregnancy-related outcomes from the safety database. Analysis of available data show no difference in the risk of overall major birth defects for SOLIRIS (0.94 per 100 live-births) compared with the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta

Congenital Defects Program (MACDP) or 2-3% in the U.K. reference population. The rate of fetal death (miscarriage and stillbirth) observed in the safety database is estimated to be 16.2%. The estimated background rate of miscarriage in clinically recognised pregnancies in the U.S. general population is 15-20%.

The background risk of birth defects for the indicated population of PNH or aHUS is not thought to be different than that in the general population. Rates of miscarriage and still birth are reported to be as high as 26% and 10% respectively in PNH. Methodological limitations of this data analysis include the use of MACDP and published literature on PNH and aHUS as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

Animal Data

In reproductive toxicology studies in mice with the murine surrogate terminal complement inhibitory antibody given during the period of organogenesis, there were no clear treatment-related findings in fetuses of mice exposed to 60 mg/kg/week, a dose comparable to the human dose of SOLIRIS on a mg/kg basis. When maternal exposure to the murine antibody occurred from the time of implantation to the end of lactation, a slightly higher number of male offspring became moribund or died in the group given 60 mg/kg/week. The relevance to use of SOLIRIS is unclear.

Use in Lactation

Although limited published data does not report detectable levels of eculizumab in human milk, maternal IgG is known to be present in human milk. Available information is insufficient to inform the effect of eculizumab on the breastfed infant. There are no data on the effects of eculizumab on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SOLIRIS and any potential adverse effects on the breastfed child from SOLIRIS or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Experience

Paroxysmal Nocturnal Haemoglobinuria (PNH)

Adult patients

The data described below reflect exposure to SOLIRIS in 196 adult patients with PNH, age 18-85, of whom 55% were female. All had signs or symptoms of intravascular haemolysis. SOLIRIS was studied in a placebo-controlled clinical study (in which 43 patients received SOLIRIS and 44, placebo); a single arm clinical study and a long term extension study. 182 patients were exposed for greater than 1 year. All patients received the recommended SOLIRIS dose regimen.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Table 4 summarises the adverse reactions that occurred at a numerically higher rate in the SOLIRIS group than the placebo group and at a rate of 5% or more among patients treated with SOLIRIS.

Table 4: **Adverse Drug Reactions*** **Reported in ≥ 2 patients in the Controlled Clinical Study**

MedDRA SOC^ Reaction	**SOLIRIS (N=43) N (%)**	**Placebo (N=44) N (%)**
Nervous System Disorders		
Headache	15 (34.9)	2 (4.5)
Gastrointestinal Disorders		
Nausea	2 (4.7)	1 (2.3)
Abdominal pain	2 (4.7)	1 (2.3)
General Disorders and Administration Site Conditions		
Fatigue	5 (12)	1 (2)
Infections and Infestations		
Oral Herpes	2 (4.7)	0 (0)
Upper respiratory tract infection	2 (4.7)	0 (0)
Skin and Subcutaneous Tissue Disorders		
Dry skin	2 (4.7)	0 (0)

*Drug-related Adverse Events occurring at a higher frequency (1 or more patients) in the SOLIRIS-treated patients relative to placebo
^ System Organ Class

In the placebo-controlled clinical study, serious adverse reactions occurred among 4 (9%) patients receiving SOLIRIS and 9 (21%) patients receiving placebo. The serious reactions included infections and progression of PNH. No deaths occurred in the study and no patients receiving SOLIRIS experienced a thrombotic event; one thrombotic event occurred in a patient receiving placebo.

Among 193 patients with PNH treated with SOLIRIS in the single arm, clinical study or the follow-up study, the adverse reactions were similar to those reported in the placebo-controlled clinical study. Serious adverse reactions occurred among 16% of the patients in these studies. The most common serious adverse reactions were: viral infection (2%), headache (2%), anaemia (2%), and pyrexia (2%).

Paediatric patients

The safety profile of paediatric patients with PNH (aged 11 years to <17 years) included in the PNH Study M07-005, appeared similar to that observed in adult patients with PNH. The most common adverse reaction reported in paediatric patients was headache.

Atypical Haemolytic Uraemic Syndrome (aHUS)

The safety of eculizumab in patients with aHUS was evaluated in 1 retrospective paediatric study (C09-001r) and 4 prospective, single-arm studies [3 in adult patients (C08-002A/B, C08-003A/B and C10-004) and 1 in paediatric patients (C10-003)]).

Adult patients

The data described below in Table 5 were derived from 78 adult patients with aHUS enrolled in Studies C08-002A/B, C08-003A/B and C10-004. Paediatric safety data are summarised in Table 7 and refer to Table 8 for additional safety data collected in 30 patients in the retrospective study C09-001r.

Table 5: Per Patient Incidence of Adverse Drug Reactions (ADRs) in ≥ 10% of Adult and Adolescent Patients Enrolled in aHUS studies C08-002A/B, C08-003A/B and C10-004, Separately and in Total

MedDRA SOC Reaction	**Number (%) of Patients**			
	C08-002 (N=17)	**C08-003 (N=20)**	**C10-004 (N=41)**	**Total (N=78)**
Blood and Lymphatic System Disorders				
Leucopaenia	2 (11.8)	2 (10.0)	0 (0.0)	4 (5.1)
Lymphopenia	0 (0.0)	2 (10.0)	0 (0.0)	2 (2.6)
Gastrointestinal Disorders				
Nausea	2 (11.8)	0 (0.0)	0 (0.0)	2 (2.6)
Vomiting	3 (17.6)	0 (0.0)	1 (2.4)	4 (5.1)
Nervous System Disorders				
Headache	1 (5.9)	3 (15.0)	0 (0.0)	4 (5.1)
Respiratory, Thoracic and Mediastinal Disorders				
Cough[a]	0 (0.0)	2 (10.0)	0 (0.0)	2 (2.6)
Vascular Disorders				
Hypertension[b]	3 (17.6)	0 (0.0)	0 (0.0)	3 (3.8)

[a.] includes preferred terms Cough and Productive Cough

[b.] includes preferred terms Hypertension and Accelerated Hypertension.

In Studies C08-002A/B, C08-003A/B and C10-004 combined, 60% (47/78) of patients experienced a serious adverse event (SAE).

The following ADRs occurred in > 1% to < 10% of adult and adolescent patients enrolled in Studies C08-002A/B, C08-003A/B and C10-004.

Table 6: Per Patient Incidence of Adverse Drug Reactions in > 1% and < 10% Adult and Adolescent Patients Enrolled in aHUS studies C08-002A/B, C08-003A/B and C10-004, Separately and in Total

MedDRA SOC Reaction		**Number (%) of Patients**		
	C08-002 (N=17)	**C08-003 (N=20)**	**C10-004 (N=41)**	**Total (N=78)**
Blood and Lymphatic System Disorders				
Abnormal clotting factor	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Anaemia	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Neutropenia	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Cardiac Disorders				
Cardiomyopathy	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Ear and Labyrinth Disorders				
Deafness bilateral	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Vertigo	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Eye Disorders				

MedDRA SOC Reaction		Number (%) of Patients		
	C08-002 (N=17)	C08-003 (N=20)	C10-004 (N=41)	Total (N=78)
Lacrimation increased	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Gastrointestinal Disorders				
Abdominal pain	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Diarrhoea	1 (5.9)	0 (0.0)	1 (2.4)	2 (2.6)
Stomatitis	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
General Disorders and Administration Site Conditions				
Asthenia	1 (5.9)	0 (0.0)	2 (4.9)	3 (3.8)
Chest discomfort	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Extravasation	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Fatigue	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Pyrexia	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Infections and Infestations				
Asymptomatic bacteriuria	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Bacterial infection	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
BK virus infection	0 (0.0)	1 (5.0)	1 (2.4)	2 (2.6)
Herpes zoster	1 (5.9)	0 (0.0)	1 (2.4)	2 (2.6)
Impetigo	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Influenza	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Meningitis meningococcal	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Meningococcal sepsis	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Nasopharyngitis	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Peritonitis	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Pneumonia	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Pyelonephritis	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Q fever	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Urinary tract infection	1 (5.9)	0 (0.0)	1 (2.4)	2 (2.6)
Investigations				
Haematocrit decreased	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Haemoglobin decreased	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Metabolism and Nutrition Disorders				
Decreased appetite	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	0 (0.0)	0 (0.0)	2 (4.9)	2 (2.6)
Pain in extremity	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Nervous System Disorders				
Paraesthesia	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Tremor	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Renal and Urinary Disorders				
Haematuria	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Reproductive System and Breast Disorders				
Menorrhagia	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnoea	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Dyspnoea exertional	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Nasal congestion	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Oropharyngeal pain	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Rhinorrhoea	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Skin and Subcutaneous Tissue Disorders				
Alopecia	0 (0.0)	1 (5.0)	2 (4.9)	3 (3.8)
Dermatitis	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)

MedDRA SOC Reaction		Number (%) of Patients		
	C08-002 (N=17)	C08-003 (N=20)	C10-004 (N=41)	Total (N=78)
Erythema	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Photosensitivity reaction	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Pruritus	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Rash[a]	0 (0.0)	0 (0.0)	2 (4.9)	2 (2.6)
Skin discolouration	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Vascular Disorders				
Hypotension	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Vein disorder	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Venous thrombosis	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)

[a] Includes rash and rash papular

Paediatric Patients

The following ADRs were reported > 10% in the paediatric aHUS Study C10-003:

- 3 (16.8%) respiratory tract infection viral (includes preferred terms: respiratory tract infection viral, viral upper respiratory tract infection and respiratory syncytial virus infection) in 1 month to < 12 yrs patients.
- 2 (11.8%) rash in 1 month to < 12 yrs patients.

Table 7 below summarises the adverse events reported in > 1% to < 10% of paediatric patients enrolled in aHUS Study C10-003.

Table 7: Per Patient Incidence of Adverse Drug Reactions in > 1% to < 10% of Paediatric Patients Enrolled in aHUS C10-003

MedDRA SOC Reaction	Number (%) of Patients	
	1 month to < 12 yrs (N=18)	Total (N=22)
Eye Disorders		
Eye discharge	1 (5.6%)	1 (4.5%)
Gastrointestinal Disorders		
Abdominal discomfort	1 (5.6%)	1 (4.5%)
Diarrhoea	1 (5.6%)	1 (4.5%)
Dyspepsia	0 (0.0)	1 (4.5%)
General Disorders and Administration Site Conditions		
Injection site rash	1 (5.6%)	1 (4.5%)
Pain	1 (5.6%)	1 (4.5%)
Infections and Infestations		
Ear infection	1 (5.6%)	1 (4.5%)
Fungal infection	1 (5.6%)	1 (4.5%)
Nasopharyngitis	1 (5.6%)	1 (4.5%)
Respiratory syncytial virus infection	1 (5.6%)	1 (4.5%)
Respiratory tract infection viral	1 (5.6%)	1 (4.5%)
Viral upper respiratory tract infection	1 (5.6%)	1 (4.5%)
Nervous System Disorders		
Headache	1 (5.6%)	1 (4.5%)
Psychiatric Disorders		
Agitation	1 (5.6%)	1 (4.5%)
Skin and Subcutaneous Tissue Disorders		
Alopecia	1 (5.6%)	1 (4.5%)

MedDRA SOC Reaction	Number (%) of Patients	
	1 month to < 12 yrs (N=18)	Total (N=22)
Dermatitis diaper	1 (5.6%)	1 (4.5%)
Eczema	1 (5.6%)	1 (4.5%)

Analysis of retrospectively collected adverse event data from paediatric and adult patients enrolled in aHUS C09-001r revealed a safety profile that was similar to that which was observed in the prospective studies. C09-001r included 19 paediatric patients less than 18 years of age.

Overall, the safety of SOLIRIS in paediatric patients with aHUS enrolled in C09-001r appeared similar to that observed in adult patients. The most common (≥ 15%) Adverse Drug Reactions occurring in paediatric patients are presented in Table 8.

Table 8: Adverse Drug Reactions occurring in ≥ 15% of Patients < 18 Years of Age Enrolled in aHUS C09-001r

MedDRA SOC Reaction	Number (%) of Patients			
	< 2 yrs (N=5)	2 to < 12 yrs (N=10)	12 to < 18yrs (N=4)	Total (N=19)
General Disorders and Administration Site Conditions				
Pyrexia	4 (80)	4 (40)	1 (25)	9 (47)
Gastrointestinal Disorders				
Diarrhoea	1 (20)	4 (40)	1 (25)	6 (32)
Vomiting	2 (40)	1 (10)	1 (25)	4 (21)
Infections and Infestations				
Upper respiratory tract infection[a]	2 (40)	3 (30)	1 (25)	6 (32)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	3 (60)	2 (20)	0 (0)	5 (26)
Nasal congestion	2 (40)	2 (20)	0 (0)	4 (21)
Cardiac Disorders				
Tachycardia	2 (40)	2 (20)	0 (0)	4 (21)

[a.] includes the preferred terms upper respiratory tract infection and nasopharyngitis.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

In Study ECU-NMO-301, 96 patients received SOLIRIS at the recommended dosage regimen and 47 patients received placebo. Patients were 19 to 75 years of age, and 91% were female.

Table 9 displays the most common adverse events from Study ECU-NMO-301 that occurred in ≥ 5% of SOLIRIS-treated patients and at a greater frequency than on placebo.

Table 9: Adverse Events Reported in 5% or More of SOLIRIS -Treated Patients in Study ECU-NMO-301 and at a Greater Frequency than in Placebo-Treated Patients

MedDRA SOC Reaction	SOLIRIS (N=96) N (%)	Placebo (N=47) N (%)
Events / Patients	1295 / 88	617 / 45

MedDRA SOC Reaction	**SOLIRIS (N=96) N (%)**	**Placebo (N=47) N (%)**
Blood and Lymphatic System Disorders		
Leucopaenia	5 (5)	1 (2)
Lymphopaenia	5 (5)	0 (0)
Eye disorders		
Cataract	6 (6)	2 (4)
Gastrointestinal Disorders		
Diarrhoea	15 (16)	7 (15)
Constipation	9 (9)	3 (6)
General Disorders and Administration Site Conditions		
Asthenia	5 (5)	1 (2)
Infections and Infestations		
Upper respiratory tract infection	28 (29)	6 (13)
Nasopharyngitis	20 (21)	9 (19)
Influenza	11 (11)	2 (4)
Pharyngitis	10 (10)	3 (6)
Bronchitis	9 (9)	3 (6)
Conjunctivitis	9 (9)	4 (9)
Cystitis	8 (8)	1 (2)
Hordeolum	7 (7)	0(0)
Sinusitis	6 (6)	0 (0)
Cellulitis	5 (5)	1 (2)
Injury, Poisoning and Procedural Complications		
Contusion	10 (10)	2 (4)
Metabolism and Nutrition Disorders		
Decreased appetite	5 (5)	1 (2)
Musculoskeletal and Connective Tissue Disorders		
Back pain	14 (15)	6 (13)
Arthralgia	11 (11)	5 (11)
Musculoskeletal pain	6 (6)	0 (0)
Muscle spasms	5 (5)	2 (4)
Nervous System Disorders		
Dizziness	14 (15)	6 (13)
Paraesthesia	8 (8)	3 (6)
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal pain	7 (7)	2 (4)
Skin and Subcutaneous Tissue Disorders		
Alopecia	5 (5)	2 (4)

Tabulated Summary of Adverse Reactions (Including Post-Marketing Experience)

Table 10 below summarises the adverse reactions observed from spontaneous reporting and in completed SOLIRIS clinical trials. The most frequent adverse reaction was headache (occurring mostly in the initial phase), and the most serious adverse reaction was meningococcal sepsis.

Adverse reactions reported at a very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), or very uncommon (<1/1000) frequency with SOLIRIS are listed by system organ class and preferred term. Adverse reactions were mostly mild to moderate in severity.

Table 10: Adverse Reactions Reported in Completed SOLIRIS Clinical Trials and in Post Marketing Reports

MedDRA SOC Reaction	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Very Uncommon (<1/1000)	Not known (cannot be estimated from the available data)
Infection and Infestations		Pneumonia, Bronchitis, Nasopharyngitis, Oral Herpes, Upper respiratory tract infection, Urinary tract infection	Meningococcal infection[a], Abscess[b], Cellulitis, Fungal infection, Infection, Influenza, Sepsis, Septic shock, Lower respiratory tract infection, Gastrointestinal infection, Cystitis, Sinusitis, Viral infection, Peritonitis, Gingivitis	Genitourinary tract gonococcal infection, Aspergillus infection[c], Arthritis bacterial[c], Haemophilus infection, Impetigo	
Neoplasms Benign, Malignant and Unspecified				Malignant melanoma, Myelodysplastic syndrome	
Blood and Lymphatic System Disorders		Leucopaenia, Anaemia	Thrombocytopenia, Lymphopenia	Haemolysis*, Abnormal clotting factor, Red blood cell agglutination, Coagulopathy	
Immune System Disorders			Anaphylactic reaction, Hypersensitivity		
Endocrine Disorders				Grave's disease	
Metabolism and Nutrition Disorders			Decreased appetite		
Psychiatric Disorders		Insomnia	Anxiety, Depression, Mood swings, Sleep disorder	Abnormal dreams	
Nervous System Disorders	Headache	Dizziness, Dysgeusia	Paraesthesia, Tremor, Syncope		
Eye Disorders			Vision blurred	Conjunctival irritation	
Ear and Labyrinth Disorders			Tinnitus, Vertigo		
Cardiac Disorders			Palpitation		
Vascular Disorders		Hypertension	Hypotension, Hot flush, Accelerated hypertension, Vein disorder	Haematoma	

MedDRA SOC Reaction	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Very Uncommon (<1/1000)	Not known (cannot be estimated from the available data)
Respiratory, Thoracic and Mediastinal Disorders		Cough, Oropharyngeal pain	Dyspnoea, Epistaxis, Throat irritation, Nasal congestion, Rhinorrhoea		
Gastrointestinal Disorders		Abdominal pain, Diarrhoea, Nausea, Vomiting	Constipation, Dyspepsia, Abdominal distension	Gastroesophageal reflux disease, Gingival pain	
Hepatobiliary Disorders			Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased	Jaundice	Liver injury[d]
Skin and Subcutaneous Tissue Disorders		Alopecia, Pruritus, Rash	Hyperhidrosis, Petechiae, Urticaria, Dry skin, Erythema, Dermatitis	Skin depigmentation	
Musculoskeletal and Connective Tissue Disorders		Arthralgia, Myalgia, Pain in extremity	Muscle spasms, Joint swelling, Back pain, Neck pain, Bone pain	Trismus	
Renal and Urinary Disorders			Renal impairment, Haematuria, Dysuria		
Reproductive System and Breast Disorders			Spontaneous penile erection	Menstrual disorder	
General Disorders and Administration Site Condition		Pyrexia, Fatigue, Influenza-like illness	Oedema, Chest discomfort, Asthenia, Chest pain, Infusion site pain, Chills	Extravasation, Infusion site paraesthesia, Feeling hot	
Investigations			Haematocrit decreased, Haemoglobin decreased	Coombs test positive[c]	
Injury, Poisoning and Procedural complication		Infusion related reaction			

*see below "Description of Selected Adverse Reactions"

[a] Meningococcal infection includes the following group of preferred terms: meningococcal infection, meningococcal sepsis, meningitis meningococcal, Neisseria infection

[b] Abscess includes the following group of preferred terms: abscess limb, colonic abscess, renal abscess, subcutaneous abscess, tooth abscess, liver abscess, perirectal abscess, rectal abscess

[c] ADRs identified in postmarketing reports

[d] Frequency cannot be estimated from the available postmarketing data

Description of Selected Adverse Reactions

In all SOLIRIS clinical studies, the most serious adverse reaction was meningococcal infection. Meningococcal infections in patients treated with SOLIRIS have presented as meningococcal sepsis. Patients should be informed of the signs and symptoms of meningococcal infection and sepsis and advised to seek medical care immediately (refer to section 4.4 – Special Warnings and Precautions for Use).

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

Cases of haemolysis have been reported in the setting of missed or delayed SOLIRIS dose in PNH clinical trials (refer to section 4. 4 – Special Warnings and Precautions for Use).

Cases of thrombotic microangiopathy (TMA) complications have been reported in the setting of missed or delayed SOLIRIS dose in aHUS clinical trials (refer to section 4.4 – Special Warnings and Precautions for Use).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No case of overdose has been reported during clinical studies. Supportive and symptomatic care should be provided in the event of overdose.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

SOLIRIS is a genetically-engineered humanised monoclonal antibody directed against the α-chain of the C5 complement protein. The antibody is a glycosylated hybrid IgG2-IgG4 kappa immunoglobulin containing human light- and heavy-chain variable region framework sequences, murine complementarity-determining region sequences, and human constant region sequences. Eculizumab is composed of two identical 448 amino acid heavy chains and two identical 214 amino acid light chains and has a molecular weight of approximately 148 kDa.

The eculizumab antibody is produced by murine myeloma cell culture and purified by standard bioprocess chromatographic technology, including specific viral inactivation and filtration steps.

Pharmacodynamic activity measured by free C5 concentrations of < 0.5 ug/mL, is correlated with essentially complete blockade of terminal complement activity in patients with PNH, aHUS, and NMOSD.

Mechanism of Action

A genetic mutation in patients with PNH leads to the generation of populations of abnormal red blood cells (known as PNH RBCs) that are deficient in terminal complement

inhibitors, rendering PNH RBCs sensitive to persistent terminal complement-mediated destruction. The subsequent intravascular haemolysis is the primary disease manifestation in patients with PNH. The destruction and loss of these PNH cells result in low blood counts (anaemia), and also fatigue, difficulty in functioning, pain, dark urine and kidney disease, shortness of breath, and blood clots.

In aHUS impairment of the regulation of the complement activity leads to uncontrolled terminal complement activation, resulting in platelet activation, endothelial cell damage and thrombotic microangiopathy. In patients with aHUS, uncontrolled terminal complement activation and the resulting complement mediated thrombotic microangiopathy are blocked with SOLIRIS treatment.

In patients with NMOSD, the exact mechanism by which eculizumab exerts its therapeutic effect is unknown but is presumed to involve inhibition of aquaporin-4 (AQP4) antibody induced terminal complement C5b-9 deposition and C5a-dependent inflammation.

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

In vitro Binding Specificity: The specificity of SOLIRIS for C5 in human serum was evaluated in two *in vitro* studies. The species specificity of SOLIRIS was assessed by determining its ability to inhibit haemolytic activity in non-human sera (4 primate and 4 non-primate species) using a complement-mediated haemolytic assay. The results of this study demonstrate that SOLIRIS does not inhibit C5 activity in sera from the species tested.

The tissue cross-reactivity of SOLIRIS 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.

Pharmacodynamics

The pharmacodynamic profile of SOLIRIS was assessed using an *in vitro* serum complement haemolysis assay that measures the extent of terminal complement inhibition in the serum of patients receiving SOLIRIS.

In patients with PNH, uncontrolled terminal complement activation and the resulting complement mediated intravascular haemolysis are blocked with SOLIRIS treatment. Administration of SOLIRIS in an initial phase/maintenance regimen of 600 mg/week for the first 4 weeks and 900 mg in the fifth week of the initial phase, followed by a 900 mg maintenance dose every other week resulted in a rapid and sustained reduction in complement-mediated haemolytic activity. SOLIRIS when administered as recommended provides a blood concentration sufficient to completely block haemolysis within 60 minutes; red blood cell destruction, as indicated by lactate dehydrogenase (LDH) levels, is significantly reduced by one week. In the Phase III study in patients with PNH, *C04-001*, the dosing regimen was sufficient to maintain plasma SOLIRIS levels to essentially

completely block terminal complement activation in 39/40 patients measured for the entire 26 week study period demonstrating that the proposed dosing regimen is adequate.

In most patients with PNH, eculizumab serum concentrations of approximately 35µg/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.

All patients treated with SOLIRIS as recommended, demonstrated rapid and sustained reduction in terminal complement activity.

In all patients with aHUS, eculizumab serum concentrations of approximately 50-100 µg/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 Trials

Adult Patients

Paroxysmal Nocturnal Haemoglobinuria (PNH)

The safety and efficacy of SOLIRIS in patients with PNH with haemolysis were assessed in a randomised, double-blind, placebo-controlled 26-week study (C04-001); patients with PNH were also treated with SOLIRIS in a single arm 52-week study (C04-002); and in a long-term extension study (E05-001). An observational non-interventional Registry for patients with PNH (M07-001) was also initiated to characterise the natural history of PNH in untreated patients and the clinical outcomes during SOLIRIS treatment.

Patients received meningococcal vaccination prior to receipt of SOLIRIS. In all studies, the dose of SOLIRIS 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. SOLIRIS was administered as an intravenous infusion over 25 - 45 minutes.

C04-001 Study (TRIUMPH)

Patients with PNH with at least 4 transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH red blood cells and platelet counts of at least 100,000/microlitre were randomised to either SOLIRIS (N=43) or placebo (N=44). Prior to randomisation, 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 stabilisation 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. Endpoints related to haemolysis included the numbers of patients achieving haemoglobin stabilisation, the number of RBC units transfused, fatigue, and health-related quality of life. To achieve a designation of haemoglobin stabilisation, a patient had to maintain a haemoglobin concentration above the haemoglobin set-point and avoid any RBC transfusion for the entire 26-week period. 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 11 below). Because of the study sample size and duration, the effects of SOLIRIS on thrombotic events could not be determined.

C04-002 Study (SHEPHERD)

Patients with PNH with at least one transfusion in the prior 24 months and at least 30,000 platelets/microlitre (μL) 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 11.

Table 11: Patient Demographics and Characteristics in C04-001 and C04-002 Studies

	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 Anaemia or MDS (%)	12 (27.3)	8 (18.7)	29 (29.9)
Patients with history of thrombosis (events)	8 (11)	9 (16)	42 (91)
Concomitant Anticoagulants (%)	20 (45.5)	24 (55.8)	59 (61)
Concomitant Steroids/Immunosuppressant Treatments (%)	16 (36.4)	14 (32.6)	46 (47.4)
Discontinued treatment	10	2	1
Packed Red Blood Cells (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)
Mean Hgb level (g/dL) at set-point (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, patients treated with SOLIRIS had significantly reduced ($p<0.001$) haemolysis resulting in improvements in anaemia as indicated by increased haemoglobin stabilisation and reduced need for RBC transfusions compared to placebo treated patients (see Table 12). 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.

In SHEPHERD, 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 12).

Table 12: Efficacy Outcomes in Studies 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 stabilised Haemoglobin levels at end of study	0	49	< 0.001	N/A	
PRBC transfused during treatment (median)	10	0	< 0.001	0.0	< 0.001
Transfusion Avoidance during treatment (%)	0	51	< 0.001	51[1]	< 0.001
				51[2]	< 0.001
LDH levels at end of study (median, U/L)	2,167	239	< 0.001	269	< 0.001
LDH Area Under the Curve (AUC) at end of study (median, U/L x Day)	411,822	58,587	< 0.001	-632,264	< 0.001
Free Haemoglobin at end of study (median, mg/dL)	62	5	< 0.001	5	< 0.001
FACIT-Fatigue (effect size) after 6 months treatment	1.13		<0.001	1.01[1]	< 0.001
FACIT-Fatigue (effect size) after 12 months treatment	N/A			1.14[2]	< 0.001

[1] Assessed after 26-week treatment in C04-002.
[2] Assessed at C04-002 study completion (52 weeks).

E05-001 Study

From the 195 patients that originated in C04-001, C04-002, or C02-001, 187 SOLIRIS-treated patients with PNH 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. Across all enrolled patients with PNH, the thrombosis rate was significantly reduced with SOLIRIS treatment as compared to the thrombosis rate prior to commencement of SOLIRIS treatment (see Table 13). However, the majority of patients received concomitant anticoagulants; the effects of anticoagulant withdrawal during SOLIRIS therapy were not studied.

Table 13: Thromboembolic Event Efficacy Outcomes

	E05-001 (All studies combined)
Pre-Treatment	
Patients (n)	195
Thromboembolic Events (n)	124
Patient Years (n)	1683.4
Thromboembolic Event Rate (n per 100 patient years)	7.37
SOLIRIS Treatment	
Patients (n)	195
Thromboembolic Events (n)	3
Patient Years (n)	281.0
Thromboembolic Event Rate (n per 100 patient years)	1.07 (P<0.001)

M07-001 (PNH Registry)

The PNH Registry (M07-001) was used to evaluate the efficacy of SOLIRIS in patients with PNH with no history of RBC transfusion and a 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.

Patients treated with SOLIRIS were observed to have a reduction in haemolysis and associated symptoms. At 6 months, patients with no history of RBC transfusion treated with SOLIRIS had significantly ($p< 0.001$) reduced LDH levels (median LDH of 305 U/L; Table 14). 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 14: Efficacy Outcomes (LDH level and FACIT-Fatigue) in Patients with PNH with No History of Transfusion in M07-001

Parameter	**SOLIRIS No transfusion**
LDH level at baseline (U/L)	(N=43) 1447
LDH level at 6 months (U/L)	(N=36) 305
FACIT-Fatigue score at baseline	(N=25) 32
FACIT-Fatigue score at last available assessment	(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 [3 in adult patients (C08-002A/B, C08-003A/B and C10-004) and 1 in paediatric patients (C10-003)] and one retrospective study with 30 patients (C09-001r) were used to evaluate the efficacy of SOLIRIS in the treatment of aHUS.

C08-002A/B and C08-003A/B

Study C08-002A/B was a prospective, single arm, 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 Plasma Exchange/Plasma Infusion (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 patients with aHUS was 900 mg every

7 ± 2 days for 4 weeks, followed by 1200 mg 7 ± 2 days later, then 1200 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 simulation that identified the recommended dose and schedule based on body weight.

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 normalisation, 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 normalisationwas defined as normalisation of platelet counts and LDH levels sustained for ≥ 2 consecutive measurements for ≥ 4 weeks. Complete TMA response was defined as haematologic normalisation and a ≥ 25% reduction in serum creatinine sustained in ≥ 2 consecutive measurements for ≥ 4 weeks. Baseline characteristics are shown in Table 15.

Table 15: 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)
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 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. The median duration of SOLIRIS therapy in Study C08-002A/B was approximately 100 weeks (range: 2 to 186 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 16 below summarises the efficacy results for 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, 2 additional patients achieved and maintained Complete TMA response due to normalisation of LDH (1 patient) and a decrease in serum creatinine (2 patients). Renal function, as measured by eGFR, was improved during SOLIRIS treatment. Four out of the 5 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).

Patients in 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. The median duration of SOLIRIS therapy in Study C08-003A/B was approximately 156 weeks (range: 26 to 182 weeks). Reduction in terminal complement activity was observed in all patients after commencement of SOLIRIS.

Table 16 below summarises the efficacy results for Study C08-003A/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, 6 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.

In both Study C08-002A/B and Study C08-003A/B, responses to SOLIRIS were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

Table 16: 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]**
Change in platelet count from baseline through week 26 ($\times 10^9$/L): Point Estimate (95% CI)	73 (40-105) *P*=0.0001	-	5 (-18, 27) *P*=0.67	-
Normalisation 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
Chronic Kidney Disease (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)

	C08-002A/B (N=17)		C08-003A/B (N=20)	
	At 26 weeks	**At 2 years[1]**	**At 26 weeks**	**At 2 years[1]**
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 normalisation: 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 SOLIRIS initiation.
[3] Study C08-003: 8 patients received ESA which was discontinued in 3 of them during SOLIRIS therapy.

C10-004

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, 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 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 SOLIRIS. Table 17 summarises the key baseline clinical and disease-related characteristics of patients enrolled in Study C10-004.

Table 17: Baseline Characteristics of Patients Enrolled in Study C10-004

Parameter	**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 (× 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 (mix, max)	10 (6, 53)

Patients in 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 Study C10-004, mean platelet count (± SD) 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 18 summarises the efficacy results for Study C10-004.

Table 18: Efficacy Outcomes for Prospective Study C10-004

Efficacy Parameter	**C10-004 (N=41) At 26 weeks**
Change in platelet count through week 26 (10^9/L)	111 (-122, 362)
Haematologic Normalisation, n (%) Median duration of haematologic normalisation, months (range)	36 (88) 15 (2, 27)
Complete TMA response, n (%) Median duration of Complete TMA response, months (range)	23 (56) 16 (1, 26)
TMA Event-free Status, n (%) 95% CI	37 (90) 77; 97
Daily TMA Intervention Rate, median (range) Before SOLIRIS treatment On SOLIRIS treatment	 0.63 (0, 1.38) 0 (0, 0.59)

Longer term treatment with SOLIRIS (median 52 weeks. ranging from 15 to 126 weeks) was associated with an increased rate of clinically meaningful improvements. When SOLIRIS treatment was continued for more than 26 weeks, 3 additional patients (63% of patients in total) achieved Complete TMA response and 4 additional patients (98% of patients in total) achieved haematologic normalisation. At the last evaluation, 25 of 41 patients (61%) achieved eGFR improvement of ≥ 15 mL/min/1.73 m^2 from baseline.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

ECU-NMO-301

Trial Design and Study Demographics

SOLIRIS was studied in a clinical trial in patients with NMOSD who were anti-aquaporin-4 (AQP4) antibody-positive.

Table 19: Summary of Patient Demographics for Study ECU-NMO-301in NMOSD

Trial Design	**Dosage and Route of Administration**	**Number of Study Subjects**	**Mean Age (years)**	**Sex**	**Historical Annualised Relapse Rate (ARR)**	**Expanded Disability Status Scale (EDSS)**
Randomised, double-blind, placebo-controlled, multicentre, Phase III	Dosage: 900 mg every 7 ± 2 days for 4 weeks, followed by 1200 mg every 14 ± 2 days Route of Administration: IV over 35 minutes	143 SOLIRIS: 96 Placebo: 47	44 Range: 19-75	Female 90.9%	SOLIRIS: Mean (SD): 1.94 (0.896) Placebo: Mean (SD): 2.07 (1.037)	SOLIRIS: Mean (SD): 4.15 (1.646) Placebo: Mean (SD): 4.26 (1.510)

The efficacy of SOLIRIS for the treatment of NMOSD was established in Study ECU-NMO-

301, a randomised, double-blind, placebo-controlled event driven trial that enrolled 143 patients with NMOSD who were anti-AQP4 antibody positive and met the following criteria at screening:

1. History of at least 2 relapses in last 12 months or 3 relapses in the last 24 months, with at least 1 relapse in the 12 months prior to screening;
2. Expanded Disability Status Scale (EDSS) score ≤ 7 (consistent with the presence of at least limited ambulation with aid);
3. If on immunosuppressive therapy (IST), on a stable dose regimen;
4. The use of concurrent corticosteroids was limited to 20 mg per day or less;
5. Patients were excluded if they had been treated with rituximab or mitoxantrone within 3 months or with IVIg within 3 weeks prior to screening.

Patients received meningococcal vaccination 2 weeks prior to initiating treatment with SOLIRIS or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. All patients who were vaccinated and met all eligibility requirements were randomised in a 2:1 ratio to the SOLIRIS group or the placebo group. A total of 96 patients were randomised to receive SOLIRIS treatment and 47 were randomised to receive placebo. Randomisation was stratified using two variables: 1) EDSS score at randomisation (Day 1) (≤ 2.0 versus ≥ 2.5 to ≤ 7); and 2) patients' prior supportive (i.e., for relapse prevention) IST and IST status at randomisation (Day 1) (treatment naïve patients versus patients continuing on the same IST(s) since last relapse versus patients with changes in IST(s) since last relapse). Patients could continue to receive a stable dose of the ISTs they were taking at the time of screening (with the exception of protocol-specified disallowed medications), but no new ISTs and no change in IST dosage were permitted during the study except for a known toxicity or adverse event associated with the given IST.

Table 20 presents the summary of IST use from baseline for patients with NMOSD enrolled in Study ECU-NMO-301.

Table 20: Summary of Immunosuppressive Therapy (IST) use at baseline in Study ECU-NMO-301

Immunosuppressive Therapy (IST) sub groups	**Placebo (N=47) N (%)**	**SOLIRIS (N=96) N (%)**	**Total (N=143) N (%)**
Steroids Alone	11 (23.4)	16 (16.7)	27 (18.9)
Azathioprine (AZA) SubGroup	13 (27.7)	37 (38.5)	50 (35.0)
AZA alone	6 (12.8)	8 (8.3)	14 (9.8)
AZA + Steroids	7 (14.9)	29 (30.2)	36 (25.2)
Mycophenolate mofetil (MMF) SubGroup	8 (17.0)	17 (17.7)	25 (17.5)
MMF alone	5 (10.6)	10 (10.4)	15 (10.5)
MMF + Steroids	3 (6.4)	7 (7.3)	10 (7.0)
Other IST(s)[a]	2 (4.3)	5 (5.2)	7 (4.9)

Other IST(s) alone	0 (0.0)	1 (1.0)	1 (0.7)
Other IST(s) + Steroids	2 (4.3)	4 (4.2)	6 (4.2)
No IST Usage	13 (27.7)	21 (21.9)	34 (23.8)

[a] Other ISTs include: cyclosporine, cyclophosphamide, methotrexate, mizoribine, and tacrolimus.

Baseline characteristics were similar between treatment groups, including mean age at first dose (43.9 in the SOLIRIS group, and 45.0 in the placebo group), and gender [91.7% female (SOLIRIS) versus 89.4% female (placebo)].

Table 21 presents the baseline characteristics of patients with NMOSD enrolled in Study ECU-NMO-301.

Table 21: Patient Disease History and Baseline Characteristics in Study ECU-NMO-301

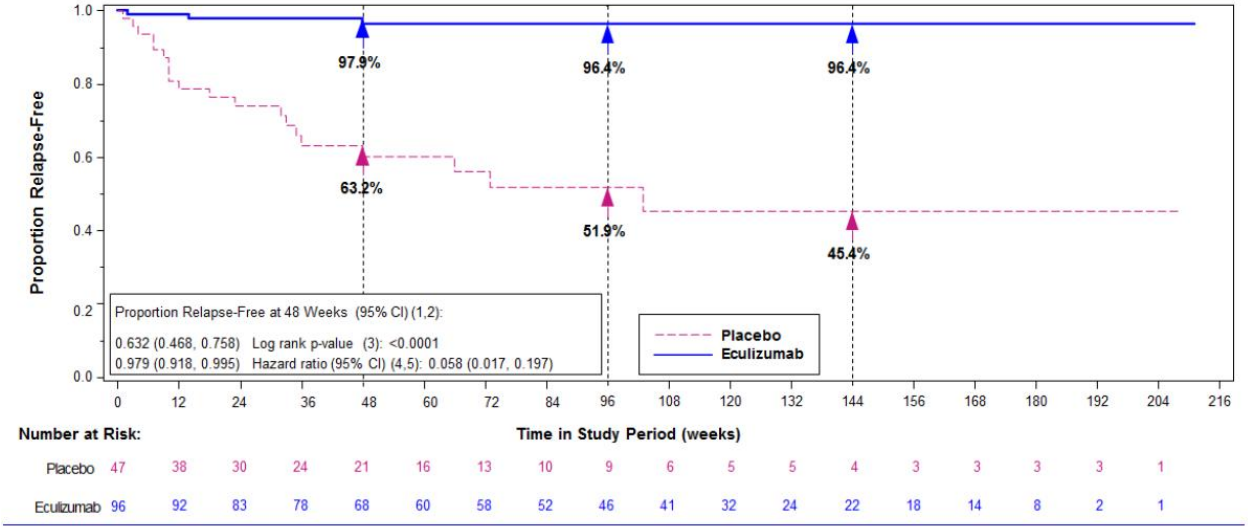
Variable	Statistic	Placebo (N=47)	SOLIRIS (N=96)	Total (N=143)
NMOSD History				
Age at NMOSD Initial Clinical Presentation (years)	Median	38.0	35.5	36.0
	Min, Max	12, 73	5, 66	5, 73
Time from NMOSD initial clinical presentation to first dose of study drug (years)	Median	3.760	5.030	4.800
	Min, Max	0.51, 29.10	0.41, 44.85	0.41, 44.85
Historical Annualised Relapse Rate (ARR) within 24 months prior to Screening	Median	1.92	1.85	1.92
	Min, Max	1.0, 6.4	1.0, 5.7	1.0, 6.4
Baseline Characteristics				
Baseline Expanded Disability Status Scale (EDSS) Score	Median	4.00	4.00	4.00
	Min, Max	1.0, 6.5	1.0, 7.0	1.0, 7.0

The primary endpoint for Study ECU-NMO-301 was the time-to-first on-trial relapse as adjudicated by an independent committee who were blinded to treatment. On-trial relapse was defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change (i.e., clinical sign) on neurologic examination that persisted for more than 24 hours as confirmed by the treating physician who was blinded to treatment. An adjudicated on-trial relapse was defined as an on-trial relapse that was positively adjudicated by the Relapse Adjudication Committee. A key secondary endpoint was the adjudicated on-trial Annualised Relapse Rate (ARR), which was computed for each patient as the number of relapses divided by the time in years.

Study Results

The time-to-first adjudicated on-trial relapse was significantly longer for patients treated with SOLIRIS compared with placebo ($p<0.0001$) (Figure 1). The hazard ratio (95% confidence interval [CI]) for SOLIRIS compared with placebo was 0.058 (0.017, 0.197), representing a 94.2% reduction in the risk of relapse.

Figure 1: Kaplan Meier Survival Estimates for Time to First Adjudicated On-trial Relapse in Study *ECU-NMO-301* – Full Analysis Set



Note: Patients who did not experience an adjudicated on-trial relapse were censored at the end of the Study Period. Stratified analyses are based on 4 randomisation strata: (1) low EDSS at randomisation (≤ 2.0), (2) high EDSS (≥ 2.5 to ≤ 7) and treatment naïve at randomization, (3) high EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomisation, (4) high EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomisation.
1 Based on the Kaplan-Meier product limit method.
2 Based on the complementary log-log transformation.
3 Based on a stratified log-rank test.
4 Based on a stratified Cox proportional hazards model.
5 Wald confidence interval.

The treatment effect on the time-to first-adjudicated on-trial relapse was observed in patients across all IST subgroups, including the subgroup with no ISTs at Baseline. During the treatment phase of the trial, 76% of patients received concomitant IST, including chronic corticosteroids; 24% of patients did not receive concomitant IST or chronic corticosteroids during the treatment phase of the trial.

The adjudicated on-trial annualized relapse rate (ARR) ratio (95% CI) for SOLIRIS compared with placebo was 0.045 (0.013, 0.151; p<0.0001), representing a 95.5% relative reduction in adjudicated ARR for patients treated with SOLIRIS compared with placebo (Table 22).

Table 22: Adjudicated On-trial Annualised Relapse Rate (ARR) – Full Analysis Set

Variable	Statistic	Placebo (N=47)	SOLIRIS (N=96)
Total number of relapses	Sum	21	3
Total number of patient-years in study period	n	52.41	171.32
Adjusted adjudicated ARR[a]	Rate	0.350	0.016
	95% CI	0.199, 0.616	0.005, 0.050
Treatment effect[a]	Rate ratio (eculizumab/placebo)	0.045	
	95% CI	0.013, 0.151	

	p-value	<0.0001

[a] Based on a Poisson regression adjusted for randomization strata and historical ARR in 24 months prior to Screening.

The annualised rate of on-trial relapse associated hospitalisation was 0.04 for SOLIRIS versus 0.31 for placebo. The annualised rate of on-trial relapse associated acute relapse treatment was 0.07 for SOLIRIS versus 0.42 for placebo (IV methylprednisolone) and 0.02 for SOLIRIS versus 0.19 for placebo (plasma exchange).

Paediatric Patients

Paroxysmal Nocturnal Haemoglobinuria (PNH)

M07-005

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 SOLIRIS at the paediatric population dosing regimen 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 SOLIRIS treatment in paediatric patients with PNH appears to be consistent with that observed in adult patients with PNH enrolled in PNH pivotal Studies (C04-001 and C04-002) (refer to Table 9 above and Table 23 below).

Table 23: 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 (children)	10.5 (6.66)	0.1250	0.0256
Change from baseline at 12 weeks of PedsQL™4.0 Generic Core scale (parents)	11.3 (8.5)	0.2500	0.0737
Change from baseline at 12 weeks of PedsQL™ Multidimensional Fatigue (children)	0.8 (21.39)	0.6250	0.4687

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

Atypical Haemolytic Uraemic Syndrome

C09-001r

A total of 15 paediatric patients (aged 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 < 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 24). No paediatric patient required new dialysis during treatment with SOLIRIS.

Table 24: Efficacy Results in Paediatric aHUS Study C09-001r

Efficacy Parameter	**< 2 yrs (N=5)**	**2 to <12 yrs (N=10)**	**12 to < 18 yrs (N=4)**	**Total (N=19)**
Platelet count normalisation, n (%)[1]	4 (80)	10 (100)	3 (75)	17 (89)
Hematologic Normalisation, n (%)	2 (40)	5 (50)	1 (25)	8 (42)
Complete TMA response, n (%)	2 (40)	5 (50)	1 (25)	8 (42)
Daily TMA intervention rate, median (range) Before eculizumab On eculizumab treatment	 1 (0, 2) < 1 (0, <1)	 < 1 (0.07, 1.46) 0 (0, < 1)	 < 1 (0, 1) 0 (0, < 1)	 0.31 (0.00, 2.38) 0.00 (0.00, 0.08)
Patients with eGFR improvement ≥ 15 mL/min/1.73 m^2, n (%)[2]	2 (40)	6 (60)	1 (25)	9 (47)

[1] Platelet count normalisation was defined as a platelet count of at least 150 X 10^9/L on at least two consecutive measurements spanning a period of at least 4 weeks.

[2] Of the 9 patients who experienced an eGFR improvement of at least 15 mL/min/1.73 m^2, one received dialysis throughout the study period and another received eculizumab as prophylaxis following renal allograft transplantation.

C10-003

A total of 22 paediatric and adolescent patients (aged 5 months to 17 years) received SOLIRIS in Study C10-003. Patients who enrolled in the study were required to have a

platelet count < lower limit of normal range, 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. Patients enrolled in Study 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 SOLIRIS. Table 25 below summarises the key baseline clinical and disease-related characteristics of patients enrolled in Study C10-003.

Table 25: Baseline Characteristics of Paediatric Patients Enrolled in 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 Study 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 platelet count (± SD) 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 median 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 SOLIRIS treatment.

Responses were similar across all ages from 5 months to 17 years of age. In Study 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 26 summarises the efficacy results for Study C10-003.

Table 26: Efficacy Outcomes in Prospective aHUS Paediatric Study C10-003

Efficacy Parameter	**1 month to < 12 years (N=18) At 26 weeks**	**All patients (N=22) At 26 weeks**
Complete haematologic normalisation, n (%) Median duration of Complete haematologic normalisation, months (range)	14 (78) 13 (7, 26)	18 (82) 14.5 (7, 26)

Efficacy Parameter	1 month to < 12 years (N=18) At 26 weeks	All patients (N=22) At 26 weeks
Complete TMA response, n (%) Median duration of Complete TMA response, months (range)	11 (61) 11 (8, 26)	14 (64) 13 (5.5, 26)
TMA Event-Free Status, n (%) 95% CI	17 (94) NA	21 (96) 77; 99
Daily TMA Intervention rate, median (range) Before SOLIRIS treatment, median On SOLIRIS treatment, median	 NA NA	 0.4 (0, 1.6) 0 (0, 0)
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

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

5.2 PHARMACOKINETIC PROPERTIES

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

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 catabolised by lysosomal enzymes to small peptides and amino acids.

Excretion

Elimination: In patients with normal kidneys, antibodies are not excreted and are excluded from filtration by their size.

The pharmacokinetics (PK) of SOLIRIS were studied in patients with PNH using total serum concentrations (free and bound drug). In 40 patients with PNH, a 1-compartmental model was used to estimate PK 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.

A second population PK analysis using a standard 1-compartmental model was conducted on the multiple dose PK data from 37 patients with aHUS 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 hours (approximately 12.4 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 patients with aHUS receiving plasma infusion or exchange.

Special Populations:

PNH

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

Paediatric patients: the pharmacokinetics of eculizumab were evaluated in Study M07-005 including 7 PNH paediatric patients (aged from 11 to < 18 years). Weight was a significant covariate resulting in lower eculizumab clearance. Dosing for paediatric patients < 40 kg is based on paediatric patients with aHUS.

aHUS

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

Paediatric patients: the second population PK model was applied to the multiple dose PK data from 22 paediatric patients with aHUS receiving the recommended SOLIRIS regimen in Study C10-003. Clearance values of SOLIRIS in paediatric patients with aHUS were 0.0104 L/h, 0.0053 L/h and 0.0022 L/h 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 378h (approximately 14.5 to 15.8 days).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies have been conducted to assess the genotoxic potential of eculizumab.

Carcinogenicity

No studies have been conducted to assess the carcinogenic potential of eculizumab.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Monobasic sodium phosphate monohydrate
Dibasic sodium phosphate heptahydrate
Sodium chloride
Polysorbate 80 (vegetable origin)
Water for Injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Do not use beyond the expiration date stamped on the carton.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

SOLIRIS vials must be stored in the original carton until time of use under refrigerated conditions at 2° to 8°C and protected from light.

SOLIRIS vials in the original package may be removed from refrigerated storage (up to 25°C) for only one single period up to 3 days. At the end of this period unopened product can be put back in the refrigerator.

DO NOT FREEZE. DO NOT SHAKE.

After dilution, the product should be used immediately. Diluted solutions of SOLIRIS are stable for 24 hours. If a diluted solution has been prepared more than 4 hours prior to administration, it should be stored at 2° to 8°C for not more than 24 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

Single unit 300 mg carton: Contains one 30 mL vial of SOLIRIS (10 mg/mL).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Product is for single use in one patient only. Discard any unused portion left in a vial, as the product contains no preservatives.

Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

Formulated at pH 7.0

CAS number

CAS registry number: 219685-50-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

Alexion Pharmaceuticals Australasia Pty Ltd
Level 4,
66 Talavera Road,
Macquarie Park NSW 2113

Medical enquiries: 1800 788 189

9 DATE OF FIRST APPROVAL

20 March 2009

10 DATE OF REVISION

16 July 2026

Summary Table of Changes

Section Changed	Summary of New Information
4.8	Addition of liver injury under adverse effects

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