AUSTRALIAN PRODUCT INFORMATION – SOLIRIS® (ECULIZUMAB *RMC)* CONCENTRATED SOLUTION FOR INTRAVENOUS INFUSION

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

- Vaccinate patients with a meningococcal vaccine prior to, or at the time of initiating Soliris; revaccinate according to current medical guidelines for vaccine use
- 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)

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).

4.2 DOSE AND METHOD OF ADMINISTRATION

Patients must be administered a meningococcal vaccine prior to, or at the time of initiation of Soliris therapy (see Section 4.4 – Special Warnings and Precautions for Use).

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

Adult patients

Paroxysmal Nocturnal Haemoglobinuria (PNH)

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

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

atypical Haemolytic Uraemic Syndrome (aHUS)

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

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

Paediatric patients (<18 years of age)

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

For paediatric PNH and aHUS patients with a body weight below 40 kg, the Soliris dosing regimen consists of:

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

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

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).

aHUS patients 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) 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 PE/PI (plasmapheresis or plasma exchange, or fresh frozen plasma infusion) as follows:

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
	≥600 mg	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	≥300 mg	300 mg per each unit of fresh frozen plasma	60 minutes prior to each 1 unit of fresh frozen plasma infusion

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 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 drug volume – refer to table below) of 0.9% Sodium Chloride Injection USP; 0.45% Sodium Chloride Injection USP; 5% Dextrose in Water Injection USP; or Ringer's Injection USP to the infusion bag.
- Do not mix with other medicinal products

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 adjust to 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.

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 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. Admixed solutions of Soliris are stable for 24 hours at 2° to 8°C and at 18° to 25°C. To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2° to 8°C for not more than 24 hours.

If an adverse reaction 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 adolescents and 4 hours in children aged less than 12 years of age. Monitor the patient for at least 1 hour following completion of the infusion for signs or symptoms of an infusion reaction.

Paediatric Population: the method of administration of Soliris is the same for all age groups.

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

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

Hepatic impairment: The safety and efficacy of Soliris have not been studied in patients with hepatic impairment.

4.3 CONTRAINDICATIONS

Hypersensitivity to eculizumab *rmc*; murine proteins; or to any of the 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 Infection

Due to its mechanism of action, the use of Soliris increases the patient's susceptibility to meningococcal infection (*Neisseria meningitidis*). Meningococcal disease due to any serogroup may occur. To reduce the risk of infection, all patients must be vaccinated against meningococcal infections prior to, or at the time of initiating Soliris. 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. Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

For patients stabilized 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 (see Section 4.4 – Special Warnings and Precautions for Use; Immunisation).

Cases of serious or fatal meningococcal infections have been reported in Soliris -treated patients. 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 (see 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 and other studies conducted with Soliris. In clinical trials, no PNH or aHUS patients experienced an infusion reaction which required discontinuation of Soliris. Soliris administration should be interrupted in all patients experiencing severe infusion reactions and appropriate medical therapy administered.

Immunogenicity

Infrequent, low titre antibody responses have been detected in Soliris -treated patients across all studies. In placebo-controlled studies low titre responses have been reported with a frequency (3.4%) similar to that of placebo (4.8%). In aHUS patients treated with Soliris, antibodies to Soliris were detected in 3/100 (3%) by the ECL bridging format assay. 1/100 (1%) of aHUS patients had low positive values for neutralizing antibodies. There has been no observed correlation of antibody development to clinical response or adverse events.

Immunisation

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

All patients must be vaccinated against meningococcal infections prior to, or at the time of initiating Soliris. 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 (see also Section 4.4 – Special Warnings and Precautions for Use). Vaccines against serogroup A, B, C, Y and W135 are recommended in minimising infection with the commonly pathogenic meningococcal serogroups.

Vaccination, particularly with a vaccine against serogroup B meningococcal infection, may further activate complement and, as a result, patients with complement-mediated diseases, including PNH and aHUS, may experience increased symptoms of their underlying disease, such as haemolysis (PNH) or TMA complications (aHUS). 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. It is recommended to vaccinate only when the underlying complement mediated disease is clinically controlled with Soliris, and when systemic eculizumab *rmc* concentrations are considered to be relatively high (i.e. within one week following a Soliris infusion).

Patients must be vaccinated or re-vaccinated according to current medical guidelines for vaccination use.

Anticoagulant Therapy

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

Laboratory Monitoring

PNH Laboratory Monitoring: PNH patients should be monitored for signs and symptoms of intravascular haemolysis, including serum lactate dehydrogenase (LDH) levels. PNH patients receiving Soliris therapy should be monitored for intravascular haemolysis by measuring LDH levels, and may require dose adjustment within the recommended 14 ± 2 day dosing schedule during the maintenance phase (up to every 12 days).

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

Monitoring after Soliris Discontinuation

Treatment Discontinuation for PNH

If PNH patients 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 clone size (in the absence of dilution due to transfusion) in one week or less; a haemoglobin level of <5 g/dL or a decrease of >4 g/dL in one week or less; angina; change in mental status; a 50% increase in serum creatinine level; or thrombosis. Monitor any patient who discontinues Soliris for at least 8 weeks to detect serious haemolysis and other reactions.

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

Treatment Discontinuation for aHUS
Thrombotic microangiopathy (TMA) complications have been observed following Soliris discontinuation in aHUS clinical studies, in some patients up to 127 weeks after discontinuation. Discontinuation of treatment is not recommended unless medically justified. Close monitoring of aHUS patients 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 aHUS patients.

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 hospitalization. Despite Soliris re-initiation following discontinuation, progression to end stage renal disease occurred in 1 patient.

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 Information Brochure and a Patient Safety Card.

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

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.

Paediatric Use

Soliris has not been studied in PNH paediatric patients who weigh less than 40 kg.

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.

Genotoxicity

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

Carcinogenicity

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

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

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy - Category B2

There are no adequate and well-controlled studies of Soliris in pregnant women. Eculizumab *rmc* is expected to cross the placenta. In animal studies with a murine anti-C5 antibody given during the period of organogenesis, there were no clearly treatment-related findings in foetuses of mice exposed to 60 mg/kg/week, a dose comparable to

the human dose of eculizumab *rmc* 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.

Soliris should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Women of childbearing potential should use adequate contraception during treatment with Soliris, and for up to 5 months after treatment.

Use in lactation

It is unknown whether eculizumab *rmc* is excreted into human milk. Since many medicinal products and immunoglobulins are secreted into human milk, and because of the potential for serious adverse reactions in nursing infants, breastfeeding should be discontinued during treatment and up to 5 months after treatment.

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

PNH

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 1 summarizes 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 1: **Adverse Drug Reactions* Reported in ≥2 patients in the Controlled Clinical Study**

Reaction	Soliris N = 43 (%)	Placebo N = 44 (%)
NERVOUS SYSTEM		
Headache	15 (34.9)	2 (4.5)
GASTROINTESTINAL		
Nausea	2 (4.7)	1 (2.3)
Abdominal pain	2 (4.7)	1 (2.3)

Reaction	Soliris N = 43 (%)	Placebo N = 44 (%)
GENERAL		
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		
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

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

aHUS

The safety of eculizumab *rmc* 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*)]).

The data described below in Table 2 were derived from 78 adult aHUS patients enrolled in Studies *C08-002A/B*, *C08-003A/B* and *C10-004*. Paediatric safety data are summarised in Table 4 and refer to Table 5 for additional safety data collected in 30 patients in the retrospective study *C09-001r*.

Table 2: 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	Number (%) of Patients			
	C08-002 (n=17)	C08-003 (n=20)	C10-004 (n=41)	Total (n=78)
Blood and Lymphatic System Disorders				
Leukopenia	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 3: 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		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				
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)

MedDRA SOC		Number (%) of Patients		
	C08-002 (n=17)	C08-003 (n=20)	C10-004 (n=41)	Total (n=78)
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)
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)

MedDRA SOC		Number (%) of Patients		
	C08-002 (n=17)	C08-003 (n=20)	C10-004 (n=41)	Total (n=78)
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 4 below summarises the adverse events reported in >1% to <10% of paediatric patients enrolled in aHUS Study *C10-003*.

Table 4: Per Patient Incidence of Adverse Drug Reactions in >1% to <10% of Paediatric Patients Enrolled in aHUS *C10-003*

MedDRA SOC	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%)
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 5.

Table 5: **Adverse Drug Reactions Occurring in ≥15% of Patients <18 Years of Age Enrolled in *aHUS C09-001r***

MedDRA SOC	Number (%) of Patients			
	<2 yrs (n=5)	2 to <12 yrs (n=10)	12 to <18 yrs (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.

Tabulated Summary of Adverse Reactions (including post-marketing experience)

Table 6 below summarises the adverse reactions observed from spontaneous reporting and in completed eculizumab *rmc* 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 eculizumab *rmc* are listed by system organ class and preferred term. Adverse reactions were mostly mild to moderate in severity.

Table 6: **Adverse Reactions Reported in Completed Eculizumab *rmc* Clinical Trials and in Post Marketing Reports**

MedDRA SOC	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Very Uncommon (<1/1,000)
Infection and infestations		Pneumonia, Bronchitis, Nasopharyngitis, Oral Herpes, Upper	Meningococcal meningitis, Abscess, Cellulitis, Fungal infection, Gingival	Genitourinary tract gonococcal infection

MedDRA SOC	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Very Uncommon (<1/1,000)
		respiratory tract infection, Urinary tract infection, Viral infection, Meningococcal sepsis, Aspergillus infection, Arthritis bacterial	infection, *Haemophilus influenza* infection, Infection, Influenza, Sepsis, Septic shock, Lower respiratory tract infection, Gastrointestinal infection, Cystitis, Neisseria infection, Sinusitis, Tooth infection, Impetigo	
Neoplasms benign, malignant and unspecified			Malignant melanoma, Myelodysplastic syndrome	
Blood and lymphatic system disorders		Thrombocytopenia, Leukopenia, Anaemia Haemolysis*	Coagulopathy, Red blood cell agglutination, Abnormal clotting factor, Lymphopenia	
Immune system disorders		Anaphylactic reaction	Hypersensitivity	
Endocrine disorders			Basedow's disease	
Metabolism and nutrition disorders		Decreased appetite	Anorexia	
Psychiatric disorders		Insomnia	Abnormal dreams, Anxiety, Depression, Mood swings, Sleep disorder	
Nervous system disorders	Headache	Dizziness, Dysgeusia, Tremor	Syncope, Paraesthesia	
Eye disorders			Conjunctival irritation, Vision blurred	
Ear and labyrinth disorders		Vertigo	Tinnitus	
Cardiac disorders			Palpitation	
Vascular disorders		Hypertension, Hypotension	Haematoma, Hot flush, Accelerated hypertension, Vein disorder	
Respiratory, thoracic and mediastinal disorders		Dyspnoea, Cough, Nasal congestion, Pharyngolaryngeal pain, Rhinorrhoea	Epistaxis, Throat irritation	

MedDRA SOC	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Very Uncommon (<1/1,000)
Gastrointestinal disorders		Abdominal pain, Constipation, Diarrhoea, Dyspepsia, Nausea, Vomiting	Abdominal distension, Gastrooesophagal reflux disease, Gingival pain, Peritonitis	
Hepatobiliary disorders			Jaundice	
Skin and subcutaneous tissue disorders		Alopecia, Pruritus, Rash	Hyperhidrosis, Petechiae, Skin depigmentation, Urticaria, Dermatitis, Dry skin, Erythema	
Musculoskeletal and connective tissue disorders		Arthralgia, Back pain, Myalgia, Neck pain, Pain in extremity, Muscle spasms, Bone pain	Joint swelling, 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		Chest discomfort, Chills, Fatigue, Asthenia, Oedema, Pyrexia, Influenza like illness	Chest pain, Infusion site paraesthesia, Infusion site pain, Feeling hot, Extravasation	
Investigations		Coombs test positive*	Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Haematocrit decreased, Haemoglobin decreased	
Injury, poisoning and procedural complication			Infusion related reaction	

**see below "selected adverse reactions"*

Description of Selected Adverse Reactions

In all eculizumab *rmc* clinical studies, the most serious adverse reaction was meningococcal sepsis, which is a common presentation of meningococcal infections in patients treated with Soliris. Patients should be informed of the signs and symptoms of

meningococcal sepsis and advised to seek medical care immediately (see 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 (see also Section 4. 4 – Special Warnings and Precautions for Use).

Cases of thrombotic microangiopathy complications have been reported in the setting of missed or delayed Soliris dose in aHUS clinical trials (see also 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 (eculizumab *rmc*) is a genetically-engineered humanized 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 *rmc* 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 *rmc* antibody is produced by murine myeloma cell culture and purified by standard bioprocess chromatographic technology, including specific viral inactivation and filtration steps.

Mechanism of action

A genetic mutation in patients with Paroxysmal Nocturnal Haemoglobinuria (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 PNH patients. 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 atypical Haemolytic Uraemic Syndrome (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 aHUS patients, uncontrolled terminal complement activation and the resulting complement mediated thrombotic microangiopathy are blocked with Soliris treatment.

Eculizumab *rmc*, 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 *rmc* 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 PNH patients, 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 PNH patients, *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 PNH patients, eculizumab *rmc* 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 aHUS patients, eculizumab *rmc* serum concentrations of approximately 50-100µg/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

Paroxysmal Nocturnal Haemoglobinuria (PNH)

The safety and efficacy of Soliris in PNH patients with haemolysis were assessed in a randomised, double-blind, placebo-controlled 26-week study (*C04-001*); PNH patients were also treated with Soliris in a single arm 52-week study (*C04-002*); and in a long-term extension study (*E05-001*). An observational non-interventional Registry for PNH patients (*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)
PNH patients with at least 4 transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH cells and platelet counts of at least 100,000/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 9g/dL in patients with symptoms and was less than or equal to 7g/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 7 below).

Because of the study sample size and duration, the effects of Soliris on thrombotic events could not be determined.

C04-002 Study (SHEPHERD)
PNH patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/microlitre 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 7.

Table 7: Patient Demographics and Characteristics in *C04-001* and *C04-002* Studies

	C04-001 Study		**C04-002 Study**
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
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 8). 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 8).

Table 8: Efficacy Outcomes in *C04-001* and *C04-002*

	C04-001 Study			**C04-002 Study**	
	Placebo N = 44	**SOLIRIS** N = 43	**P-Value**	**SOLIRIS** N = 97	**P-Value**

	C04-001 Study			C04-002 Study	
	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 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 PNH patients were enrolled in a long-term extension study (*E05-001*). All patients sustained a reduction in intravascular haemolysis over a total Soliris exposure time ranging from 10 to 54 months. Across all enrolled PNH patients, the thrombosis rate was significantly reduced with Soliris treatment as compared to the thrombosis rate prior to commencement of Soliris treatment (see Table 9). However, the majority of patients received concomitant anticoagulants; the effects of anticoagulant withdrawal during Soliris therapy were not studied.

Table 9: **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 PNH patients 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 10Table). 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 10: 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 aHUS patients 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 normalization, complete TMA response, changes in LDH, renal function and quality of life. TMA-event free status was defined as the absence for at least 12 weeks of the following: decrease in platelet count of >25% from baseline, PE/PI, and new dialysis. TMA interventions were defined as PE/PI or new dialysis. Haematologic normalization was defined as normalization of platelet counts and LDH levels sustained for ≥2 consecutive measurements for ≥4 weeks. Complete TMA response was defined as haematologic normalization and a ≥25% reduction in serum creatinine sustained in ≥2 consecutive measurements for ≥4 weeks. Baseline characteristics are show in Table 11.

Table 11: **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 12 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 12 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 12: 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	-
Normalization of platelet count All patients, n (%) (95% CI) Patients with abnormal baseline, n/n (%)	14 (82) (57, 96) 13/15, (87)	15 (88) (64, 99) 13/15, (87)	18 (90) (68, 99) 1/3 (33)	18 (90) (68, 99) 1/3 (33)
TMA event-free status: n (%) (95% CI)	15 (88) (64, 99)	15 (88) (64, 99)	16 (80) (56, 94)	19 (95) (75, 99)
TMA intervention rate Daily pre-eculizumab rate, median (min, max) Daily during-eculizumab rate, median (min, max) *P*-value	0.88 (0.04, 1.59) 0 (0, 0.31) *P*<0.0001	0.88 (0.04, 1.59) 0 (0, 0.31) *P*<0.0001	0.23 (0.05, 1.09) 0 *P* <0.0001	0.23 (0.05, 1.09) 0 *P* <0.0001
CKD improvement by ≥1 stage: n (%) (95% CI)	10 (59) (33, 82)	12 (71) (44, 90)	7 (35) (15, 59)	12 (60) (36, 81)

	C08-002A/B N = 17		C08-003A/B N = 20	
	At 26 weeks	**At 2 years[1]**	**At 26 weeks**	**At 2 years[1]**
eGFR change mL/min/1.73 m^2: median (range)	20 (-1,98)	28 (3, 82)	5 (-1, 20)	11 (-42, 30)
eGFR improvement ≥ 15 mL / min / 1.73 m^2 : n (%) (95% CI)	8 (47) (23, 72)	10 (59) (33, 82)	1 (5) (0, 25)	8 (40) (19, 64)
Change in Hgb > 20g/L: n (%) (95% CI)	11 (65) (38, 86)[2]	13 (76) (50, 93)	9 (45) (23, 68)[3]	13 (65) (41, 85)
Haematologic normalization: n (%) (95% CI)	13 (76) (50, 93)	15 (88) (64, 99)	18 (90) (68, 99)	18 (90) (68, 99)
Complete TMA response: n (%) (95% CI)	11 (65) (38, 86)	13 (76) (50, 93)	5 (25) (9, 49)	11 (55) (32, 77)

[1] At data cut-off (20 April 2012)
[2] Study C08-002: 3 patients received ESA which was discontinued after eculizumab *rmc* initiation.
[3] Study C08-003: 8 patients received ESA which was discontinued in 3 of them during eculizumab *rmc* 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 13 summarises the key baseline clinical and disease-related characteristics of patients enrolled in *Study C10-004*.

Table 13: **Baseline Characteristics of Patients Enrolled in Study C10-004**

Parameter	**Study C10-004 n=41**
Time from aHUS diagnosis to first study dose (months), median (min, max)	0.79 (0.03, 311)
Time from current clinical TMA manifestation until first study dose (months), median (min, max)	0.52 (0.03, 19)
Baseline platelet count (× 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 14 summarises the efficacy results for *Study C10-004*.

Table 14: **Efficacy Outcomes for Prospective Study *C10-004***

Efficacy Parameter	**Study C10-004 (N = 41)** At 26 weeks
Change in platelet count through week 26 (10^9/L)	111 (-122, 362)
Haematologic Normalization, n (%) Median duration of haematologic normalization, 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.

Paediatric Population

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 PNH patients appears to be consistent with that observed in adult PNH patients enrolled in PNH pivotal Studies (*C04-001 and C04-002*) (refer to Table 8 above and Table 15 below).

Table 15: **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
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 16). No paediatric patient required new dialysis during treatment with Soliris.

Table 16: 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 normalization, n (%)[1]	4 (80)	10 (100)	3 (75)	17 (89)
Hematologic Normalization, 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 150,000 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 17 below summarises the key baseline clinical and disease-related characteristics of patients enrolled in *Study C10-003*.

Table 17: **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 18 summarises the efficacy results for *Study C10-003*.

Table 18: **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)
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 m2 from baseline. No patient required new dialysis with Soliris.

5.2 PHARMACOKINETIC PROPERTIES

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

Metabolism

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

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 PNH patients 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 aHUS patients receiving the recommended Soliris regimen in studies *C08-002A/B* and *C08-003A/B*. In this model, the clearance of Soliris for a typical aHUS patient weighing 70 kg was 0.0139 L/hr and the volume of distribution was 5.6 L. The elimination half-life was 297 h (approximately 12.4 days).

The clearance and half-life of eculizumab *rmc* were also evaluated during plasma exchange interventions. Plasma exchange resulted in an approximately 50% decline in eculizumab *rmc* concentrations following a 1 hour intervention and the elimination half-life of eculizumab *rmc* was reduced to 1.3 hours. Supplemental dosing is recommended when Soliris is administered to aHUS patients 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 *rmc* was 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 *rmc* clearance. Dosing for paediatric patients <40 kg is based on paediatric patients with aHUS.

aHUS

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

Paediatric patients: the second population PK model was applied to the multiple dose PK data from 22 paediatric aHUS patients receiving the recommended Soliris regimen in Study *C10-003*. Clearance values of Soliris in paediatric aHUS patients 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 *rmc*.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Monobasic sodium phosphate monohydrate, 13.8 mg
Dibasic sodium phosphate heptahydrate, 53.4 mg
Sodium chloride, 263.1 mg
Polysorbate 80 (vegetable origin), 6.6 mg
Water for Injection

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. Store in the original package in order to protect from light.

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

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9 DATE OF FIRST APPROVAL

20 March 2009

10 DATE OF REVISION

09 JUL 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Initial reformat of PI
4.4	Additional information added regarding other Neisseria species reported including gonococcal infections
4.5	to include information on the potential for chronic human IVIg treatment to interfere with serum eculizumab concentrations
4.8	update to ADR table – five ADRs increased in frequency; addition of a preferred term
	to provide information on meningococcal sepsis as common presentation of meningococcal infections in Soliris treated patients

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