ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Soliris 300 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One vial of 30 ml contains 300 mg of eculizumab (10 mg/ml).

After dilution, the final concentration of the solution to be infused is 5 mg/ml.

Excipients with known effect: Sodium (5 mmol per vial)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colorless, pH 7.0 solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Soliris is indicated in adults and children for the treatment of:
- Paroxysmal nocturnal haemoglobinuria (PNH).
  Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1).
- Atypical haemolytic uremic syndrome (aHUS) (see section 5.1).

Soliris is indicated in adults for the treatment of:
- Refractory generalized myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive (see section 5.1).

4.2 Posology and method of administration

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

Posology

Adult Patients:

In Paroxysmal Nocturnal Haemoglobinuria (PNH):
The PNH dosing regimen for adult patients (≥18 years of age) consists of a 4-week initial phase followed by a maintenance phase:
- Initial phase: 600 mg of Soliris administered via a 25 – 45 minute intravenous infusion every week for the first 4 weeks.

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

In atypical Haemolytic Uremic Syndrome (aHUS) and refractory generalized Myasthenia Gravis (gMG):
The aHUS and refractory gMG dosing regimen for adult patients (≥18 years of age) consists of a 4 week initial phase followed by a maintenance phase:
- Initial phase: 900 mg of Soliris administered via a 25 – 45 minute intravenous infusion every week for the first 4 weeks.
- Maintenance phase: 1,200 mg of Soliris administered via a 25 – 45 minute intravenous infusion for the fifth week, followed by 1,200 mg of Soliris administered via a 25 – 45 minute intravenous infusion every 14 ± 2 days (see section 5.1).

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

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

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

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

Soliris has not been studied in paediatric patients with refractory gMG.

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

Type of Plasma Intervention	**Most Recent Soliris Dose**	**Supplemental Soliris Dose With Each PE/PI Intervention**	**Timing of Supplemental Soliris Dose**
Plasmapheresis or 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 infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

Treatment monitoring
aHUS patients should be monitored for signs and symptoms of thrombotic microangiopathy (TMA) (see section 4.4 aHUS laboratory monitoring).

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

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

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

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

Method of administration
Do not administer as an intravenous push or bolus injection. Soliris should only be administered via intravenous infusion as described below.

For instructions on dilution of the medicinal product before administration, see section 6.6.
The diluted solution of Soliris should be administered by intravenous infusion over 25 – 45 minutes in adults and 1-4 hours in paediatric patients via gravity feed, a syringe-type pump, or an infusion pump. It is not necessary to protect the diluted solution of Soliris from light during administration to the patient.
Patients should be monitored for one hour following infusion. If an adverse event occurs during the administration of Soliris, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time may not exceed two hours in adults and adolescents (aged 12 years to under 18 years) and four hours in children aged less than 12 years.

Refractory gMG
Available data suggest that clinical response is usually achieved by 12 weeks of Soliris treatment. Discontinuation of the therapy should be considered in a patient who shows no evidence of therapeutic benefit by 12 weeks.

4.3 Contraindications

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

Soliris therapy must not be initiated in patients (see section 4.4):
- with unresolved *Neisseria meningitidis* infection
- who are not currently vaccinated against *Neisseria meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.

4.4 Special warnings and precautions for use

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

Meningococcal Infection
Due to its mechanism of action, the use of Soliris increases the patient's susceptibility to meningococcal infection (*Neisseria meningitidis*). Meningococcal disease due to any serogroup may occur. To reduce the risk of infection, all patients must be vaccinated at least 2 weeks prior to receiving Soliris unless the risk of delaying Soliris therapy outweighs the risks of developing a meningococcal infection. Patients who initiate Soliris treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y, W 135 and B where available, are recommended in preventing the commonly pathogenic meningococcal serogroups. Patients must receive vaccination according to current national vaccination guidelines for vaccination use.

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

Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents. Cases of serious or fatal meningococcal infections have been reported in Soliris-treated patients. All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary. Patients should be informed of these signs and symptoms and steps taken to seek medical care immediately. Physicians must discuss the benefits and risks of Soliris therapy with patients and provide them with a patient information brochure and a patient safety card (see Package Leaflet for a description).

Other Systemic Infections

Due to its mechanism of action, Soliris therapy should be administered with caution to patients with active systemic infections. Patients may have increased susceptibility to infections, especially with encapsulated bacteria. Patients should be provided with information from the Package Leaflet to increase their awareness of potential serious infections and the signs and symptoms of them.

Infusion Reactions

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

Immunogenicity

Infrequent antibody responses have been detected in Soliris-treated patients across all clinical studies. In PNH placebo controlled studies low antibody responses have been reported with a frequency (3.4%) similar to that of placebo (4.8%).
In patients with aHUS treated with Soliris, antibodies to Soliris were detected in 3/100 (3%) by the ECL bridging format assay. 1/100 (1%) aHUS patients had low positive values for neutralizing antibodies.
In a refractory gMG placebo controlled study, none (0/62) of the Soliris treated patients showed antidrug antibody response during the 26 week active treatment.
There has been no observed correlation of antibody development to clinical response or adverse events.

Immunization

Prior to initiating Soliris therapy, it is recommended that PNH, aHUS, and refractory gMG patients initiate immunizations according to current immunization guidelines. Additionally, all patients must be vaccinated against meningococcal infections at least 2 weeks prior to receiving Soliris unless the risk of delaying Soliris therapy outweighs the risks of developing a meningococcal infection. Patients who initiate Soliris treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y, W 135 and B where available are recommended in preventing the commonly pathogenic meningococcal serogroups. (see Meningococcal Infection).

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

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

Anticoagulant therapy
Treatment with Soliris should not alter anticoagulant management.

Immunosuppressant and anticholinesterase therapies
Patients in refractory gMG clinical trials continued treatment with immunosuppressant and anticholinesterase therapies while on Soliris treatment. Withdrawal of immunosuppressant and anticholinesterase therapies during Soliris treatment for refractory gMG was not assessed in the placebo-controlled studies.
In the open-label extension trial (Study ECU-MG-302), physicians had the option to adjust background immunosuppressant therapies. In this setting, a decrease of the daily dose of at least 1 immunosuppressant was observed in 47% of patients. The most common reason for change in immunosuppressant therapy was improvement in MG symptoms while on eculizumab treatment. When immunosuppressant and anticholinesterase therapies are decreased or discontinued, patients should be monitored closely for signs of disease exacerbation.

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

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

Treatment Discontinuation for PNH
If PNH patients discontinue treatment with Soliris they should be 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 as early as 4 weeks and up to 127 weeks following discontinuation of Soliris treatment in some patients. Discontinuation of treatment should only be considered if medically justified.

In aHUS clinical studies, 61 patients (21 paediatric patients) discontinued Soliris treatment with a median follow-up period of 24 weeks. Fifteen severe thrombotic microangiopathy (TMA) complications in 12 patients were observed following treatment discontinuation, and 2 severe TMA complications occurred in an additional 2 patients that received a reduced dosing regimen of Soliris outside of the approved dosing regimen (See Section 4.2). Severe TMA complications occurred in

patients regardless of whether they had an identified genetic mutation, high risk polymorphism or auto-antibody. Additional serious medical complications occurred in these patients including severe worsening of kidney function, disease-related hospitalization and progression to end stage renal disease requiring dialysis. Despite Soliris re-initiation following discontinuation, progression to end stage renal disease occurred in one patient.

If aHUS patients discontinue treatment with Soliris, they should be monitored closely for signs and symptoms of severe thrombotic microangiopathy complications. Monitoring may be insufficient to predict or prevent severe thrombotic microangiopathy complications in patients with aHUS after discontinuation of Soliris.
Severe thrombotic microangiopathy complications post discontinuation can be identified by (i) any two, or repeated measurement of any one, of the following: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during Soliris treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during Soliris treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during Soliris treatment; or (ii) any one of the following: a change in mental status or seizures; angina or dyspnoea; or thrombosis.

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

Treatment discontinuation for refractory gMG:
Use of Soliris in refractory gMG treatment has been only studied in the setting of chronic administration. Patients that discontinue Soliris treatment should be carefully monitored for signs and symptoms of deterioration of disease.

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

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

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

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

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

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

Fertility
No specific study of eculizumab on fertility has been conducted.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
Supportive safety data were obtained from 29 completed and one ongoing clinical studies that included 1,407 patients exposed to eculizumab in ten disease populations, including PNH, aHUS, and refractory gMG. The most common adverse reaction was headache, (occurred mostly in the initial phase), and, of all meningococcal infections[a] the most frequently reported serious adverse reaction was meningococcal sepsis.

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

Table 1: Adverse Reactions reported in 1,407 patients included in overall eculizumab clinical trials, including patients with PNH, aHUS, and refractory gMG as well as from postmarketing experience

MedDRA System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
Infection and infestations		Pneumonia, Upper respiratory tract infection, Nasopharyngitis, Urinary tract infection, Oral Herpes	Meningococcal infection[a], Sepsis, Septic shock, Peritonitis, Lower respiratory tract infection, Fungal infection, Viral infection, Bronchitis, Abscess, Cellulitis, Influenza, Gastrointestinal infection, Cystitis, Infection, Sinusitis, Tooth infection	Aspergillus infection[b], Arthritis bacterial[b], Genitourinary tract gonococcal infection, Haemophilus influenzae infection, Impetigo, Gingivitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)				Malignant melanoma, Myelodysplastic syndrome
Blood and lymphatic system disorders		Leukopenia, Anaemia	Thrombocytopenia, Lymphopenia	Haemolysis*, Abnormal clotting factor, Red blood cell agglutination, Coagulopathy
Immune system disorders			Anaphylactic reaction, Hypersensitivity	
Endocrine disorders				Basedow's disease
Metabolism and nutrition disorders			Decreased appetite	
Psychiatric disorders		Insomnia	Depression, Anxiety, Mood swings	Abnormal dreams, Sleep disorder
Nervous system disorders	Headache	Dizziness, Dysgeusia, Tremor	Paraesthesia	Syncope
Eye disorders			Vision blurred	Conjunctival irritation
Ear and labyrinth disorders			Tinnitus, Vertigo	
Cardiac disorders			Palpitation	
Vascular disorders		Hypertension	Accelerated hypertension, Hypotension, Hot flush, Vein disorder	Haematoma
Respiratory, thoracic and mediastinal disorders		Cough, Oropharyngeal pain	Dyspnoea, Epistaxis, Throat irritation, Nasal congestion, Rhinorrhoea	
Gastrointestinal disorders		Diarrhoea, Vomiting, Nausea, Abdominal pain	Constipation, Dyspepsia, Abdominal distension	Gastroesophageal reflux disease, Gingival pain
Hepatobiliary disorders				Jaundice
Skin and subcutaneous tissue disorders		Rash, Pruritus, Alopecia	Urticaria, Erythema, Petechiae, Hyperhidrosis, Dry skin	Dermatitis, Skin depigmentation
Musculoskeletal and connective tissue		Arthralgia, Myalgia, Pain in extremity	Muscle spasms, Bone pain, Back pain, Neck	Trismus

disorders			pain, Joint swelling	
Renal and urinary disorders			Renal impairment, Dysuria	Haematuria
Reproductive system and breast disorders			Spontaneous penile erection, Menstrual disorder	
General disorders and administration site conditions		Pyrexia, Chills, Fatigue, Influenza like illness	Oedema, Chest discomfort, Asthenia, Chest pain, Infusion site pain	Extravasation, Infusion site paraesthesia, Feeling hot
Investigations			Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Haematocrit decreased, Haemoglobin decreased	Coombs test positive[b]
Injury, poisoning and procedural complication			Infusion related reaction	

**See paragraph Description of selected adverse reactions*
[a]=Meningococcal infection includes the following group of PTs: Meningococcal sepsis, Meningococcal meningitis, Neisseria infection; [b] = Adverse reactions identified in postmarketing reports;

Description of selected adverse reactions
In all clinical studies, including PNH and aHUS clinical trials, the most serious adverse reaction was meningococcal septicaemia (see section 4.4). No meningococcal infections were reported in completed refractory gMG clinical studies.

Antibodies to Soliris were detected in 2% of patients with PNH using an ELISA assay and 3% of patients with aHUS using the ECL bridging format assay. In refractory gMG placebo-controlled studies, no antidrug antibodies were observed. As with all proteins there is a potential for immunogenicity.

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

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

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

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

Soliris has not been studied in paediatric patients with refractory gMG.

Elderly population

No overall differences in safety were reported between elderly (≥ 65 years) and younger refractory gMG patients (< 65 years) (see section 5.1).

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA25

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

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

Mechanism of action

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

In PNH patients, uncontrolled terminal complement activation and the resulting complement-mediated intravascular haemolysis are blocked with Soliris treatment.
In most PNH patients, eculizumab serum concentrations of approximately 35 microgram/mL are sufficient for essentially complete inhibition of terminal complement-mediated intravascular haemolysis.
In PNH, chronic administration of Soliris resulted in a rapid and sustained reduction in complement-mediated haemolytic activity.

In aHUS patients, uncontrolled terminal complement activation and the resulting complement-mediated thrombotic microangiopathy are blocked with Soliris treatment.
All patients treated with Soliris when administered as recommended demonstrated rapid and sustained reduction in terminal complement activity. In all aHUS patients, eculizumab serum concentrations of approximately 50 - 100 microgram/mL are sufficient for essentially complete inhibition of terminal complement activity.
In aHUS, chronic administration of Soliris resulted in a rapid and sustained reduction in complement-mediated thrombotic microangiopathy.

In refractory gMG patients, uncontrolled terminal complement activation causes membrane attack complex (MAC) dependent lysis and C5a-dependent inflammation at the Neuromuscular Junction (NMJ) leading to failure of neuromuscular transmission. Chronic administration of Soliris results in immediate, complete, and sustained inhibition of terminal complement activity.

Clinical efficacy and safety

Paroxysmal Nocturnal Haemoglobinuria

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

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

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

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

Parameter	C04-001		C04-002
	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)
Concomitant Anticoagulants (%)	20 (45.5)	24 (55.8)	59 (61)

Parameter	C04-001		C04-002
	Placebo N = 44	**Soliris** N = 43	**Soliris** N = 97
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 setpoint (SD)	7.7 (0.75)	7.8 (0.79)	N/A
Pre-treatment LDH levels (median, U/L)	2,234.5	2,032.0	2,051.0
Free Haemoglobin at baseline (median, mg/dL)	46.2	40.5	34.9

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

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

	C04-001			C04-002*	
	Placebo N = 44	**Soliris** N = 43	**P – Value**	**Soliris** N = 97	**P – Value**
Percentage of patients with stabilized Haemoglobin levels at end of study	0	49	< 0.001	N/A	
PRBC transfused during treatment (median)	10	0	< 0.001	0	< 0.001
Transfusion Avoidance during treatment (%)	0	51	< 0.001	51	< 0.001
LDH levels at end of study (median, U/L)	2,167	239	< 0.001	269	< 0.001
LDH AUC at end of study (median, U/L x Day)	411,822	58,587	< 0.001	-632,264	< 0.001
Free Haemoglobin at end of study (median, mg/dL)	62	5	< 0.001	5	< 0.001
FACIT-Fatigue (effect size)		1.12	< 0.001	1.14	< 0.001

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

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

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

In the PNH Registry, patients treated with Soliris were observed to have a reduction in haemolysis and associated symptoms. At 6 months, patients treated with Soliris with no history of RBC transfusion had significantly ($p<0.001$) reduced LDH levels (median LDH of 305 U/L; Table 4). Furthermore, 74% of the patients without a history of transfusion and treated with Soliris experienced clinically meaningful improvements in FACIT-Fatigue score (i.e., increase by 4 points or more) and 84% in EORTC fatigue score (i.e., decrease by 10 points or more).

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

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

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

Atypical Haemolytic Uremic Syndrome

Data from 100 patients in four prospective controlled studies, three in adult and adolescent patients (C08-002A/B C08-003A/B, C10-004) one in paediatric and adolescent patients (C10-003) and 30 patients in one retrospective study (C09-001r) were used to evaluate the efficacy of Soliris in the treatment of aHUS.

Study C08-002A/B was a prospective, controlled, open-label study which accrued patients in the early phase of aHUS with evidence of clinical thrombotic microangiopathy manifestations with platelet count $\leq 150 \times 10^9$/L despite PE/PI, and LDH and serum creatinine above upper limits of normal. Study C08-003A/B was a prospective, controlled, open-label study which accrued patients with longer term aHUS without apparent evidence of clinical thrombotic microangiopathy manifestations and receiving chronic PE/PI (≥1 PE/PI treatment every two weeks and no more than 3 PE/PI treatments/week for at least 8 weeks before the first dose). Patients in both prospective studies were treated with Soliris for 26 weeks and most patients enrolled into a long-term, open-label extension study. All patients enrolled in both prospective studies had an ADAMTS-13 level above 5%.

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

Primary endpoints included platelet count change from baseline in study C08-002A/B and thrombotic microangiopathy (TMA) event-free status in study C08-003A/B. Additional endpoints included TMA intervention rate, haematologic normalization, complete TMA response, changes in LDH, renal function and quality of life. TMA-event free status was defined as the absence for at least 12 weeks of the following: decrease in platelet count of > 25% from baseline, PE/PI, and new dialysis. TMA

interventions were defined as PE/PI or new dialysis. Haematologic normalization was defined as normalization of platelet counts and LDH levels sustained for ≥2 consecutive measurements for ≥4 weeks. Complete TMA response was defined as haematologic normalization and a ≥25% reduction in serum creatinine sustained in ≥ 2 consecutive measurements for ≥ 4 weeks.
Baseline characteristics are shown in Table 5.

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

Parameter	**C08-002A/B**	**C08-003A/B**
	Soliris N = 17	**Soliris** N = 20
Time from first diagnosis until screening in months, median (min, max)	10 (0.26, 236)	48 (0.66, 286)
Time from current clinical TMA manifestation until screening in months, median (min, max)	< 1 (<1, 4)	9 (1, 45)
Number of PE/PI sessions for current clinical TMA manifestation, median (min, max)	17 (2, 37)	62 (20, 230)
Number of PE/PI sessions in 7 days prior to first dose of eculizumab, median (min, max)	6 (0, 7)	2 (1, 3)
Baseline platelet count ($\times 10^9$/L), mean (SD)	109 (32)	228 (78)
Baseline LDH (U/L), mean (SD)	323 (138)	223 (70)
Patients without identified mutation, n (%)	4 (24)	6 (30)

Patients in aHUS Study C08-002 A/B received Soliris for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients continued to receive Soliris by enrolling into an extension study. In aHUS Study C08-002A/B, the median duration of Soliris therapy was approximately100 weeks (range: 2 weeks to 145 weeks).
A reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Soliris. Reduction in terminal complement activity was observed in all patients after commencement of Soliris. Table 6 summarizes the efficacy results for aHUS Study C08-002A/B. All rates of efficacy endpoints improved or were maintained through 2 years of treatment. Complete TMA response was maintained by all responders. When treatment was continued for more than 26 weeks, two additional patients achieved and maintained Complete TMA response due to normalization of LDH (1 patient) and a decrease in serum creatinine (2 patients).
Renal function, as measured by eGFR, was improved and maintained during Soliris therapy. Four of the five patients who required dialysis at study entry were able to discontinue dialysis for the duration of Soliris treatment, and one patient developed a new dialysis requirement. Patients reported improved health-related quality of life (QoL).

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

Patients in aHUS study C08-003A/B received Soliris for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients continued to receive Soliris by enrolling into an extension study. In aHUS Study C08-003A/B, the median duration of Soliris therapy was approximately 114 weeks (range: 26 to 129 weeks). Table 6 summarizes the efficacy results for aHUS Study C08-003A/B.
In aHUS Study C08-003A/B, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins. Reduction in terminal complement activity was observed in all patients after commencement of Soliris. All rates of efficacy endpoints improved or were maintained through 2 years of treatment. Complete TMA response was maintained by all responders. When treatment was continued for more than 26 weeks, six additional patients achieved and maintained Complete TMA response due to a decrease in serum creatinine. No patient required new dialysis with Soliris. Renal function, as measured by median eGFR, increased during Soliris therapy.

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

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

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

aHUS Study C10-004 enrolled 41 patients who displayed signs of thrombotic microangiopathy (TMA). In order to qualify for enrolment, patients were required to have a platelet count < lower limit of normal range (LLN), evidence of haemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. The median patient age was 35 (range: 18 to 80 years). All patients enrolled in aHUS Study C10-004 had an ADAMTS-13 level above 5%. Fifty-one percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 35 patients received PE/PI prior to eculizumab. Table 7 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in aHUS C10-004.

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

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

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

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

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

Efficacy Parameter	aHUS Study C10-004 **(N = 41)** At 26-weeks
Change in platelet count through week 26 (10^9/L)	111 (-122, 362)
Hematologic Normalization, n (%) Median duration of hematologic normalization, weeks (range) [1]	36 (88) 46 (10, 74)
Complete TMA response, n (%) Median duration of complete TMA response, weeks (range) [1]	23 (56) 42 (6, 74)
TMA Event-free Status, n (%) 95% CI	37 (90) 77; 97
Daily TMA Intervention Rate, median (range) Before eculizumab On eculizumab treatment	 0.63 (0, 1.38) 0 (0, 0.58)

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

Longer term treatment with Soliris (median 52 weeks ranging from 15 to 126 weeks) was associated with an increased rate of clinically meaningful improvements in adult patients with aHUS. When Soliris treatment was continued for more than 26 weeks, three additional patients (63% of patients in total) achieved Complete TMA response and four additional patients (98% of patients in total)

achieved hematologic normalization. At the last evaluation, 25 of 41 patients (61%) achieved eGFR improvement of ≥ 15 mL/min/1.73 m^2 from baseline.

Refractory Generalized Myasthenia Gravis

Data from 139 patients in two prospective controlled studies (Studies C08-001 and ECU-MG-301), and one open-label extension trial (Study ECU-MG-302) were used to evaluate the efficacy of Soliris in the treatment of patients with refractory gMG.

Study ECU-MG-301 (REGAIN) was a 26-week double-blind, randomized, placebo-controlled, multi-center Phase 3 study of Soliris in patients who had failed previous therapies and remain symptomatic. One hundred and eighteen (118) of the 125 (94%) patients completed the 26-week treatment period and 117 (94%) patients subsequently enrolled in Study ECU-MG-302, an open-label, multi-center long-term safety and efficacy extension study in which all patients received Soliris treatment.

In Study ECU-MG-301, gMG patients with a positive serologic test for anti-AChR antibodies, MGFA (Myasthenia Gravis Foundation of America) clinical classification class II to IV and MG-ADL total score ≥6 were randomized to either Soliris (n = 62) or placebo (n = 63). All patients included in the trial were refractory gMG patients and met the following predefined criteria:

1) Failed treatment for at least one year with 2 or more immunosuppressant therapies (either in combination or as monotherapy), ie, patients continued to have impairment in activities of daily living despite immunosuppressant therapies

OR

2) Failed at least one immunosuppressant therapy and required chronic plasma exchange or IVIg to control symptoms, ie, patients require PE or IVIg on a regular basis for the management of muscle weakness at least every 3 months over previous 12 months.

Patients received meningococcal vaccination prior to initiating treatment with Soliris or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. In Studies ECU-MG-301 and ECU-MG-302, the dose of Soliris in adult refractory gMG patients was 900 mg every 7 ± 2 days for 4 weeks, followed by 1200 mg at Week 5± 2 days, then 1,200 mg every 14 ± 2 days for the study duration. Soliris was administered as an intravenous infusion over 35 minutes.

Table 9 presents the baseline characteristics of the refractory gMG patients enrolled in Study ECU-MG-301.

Table 9: Patient Demographic and Characteristics in Study ECU-MG-301

	Soliris (n=62)	Placebo (n=63)
Age at MG Diagnosis (years), Mean (min, max)	38.0 (5.9, 70.8)	38.1 (7.7, 78.0)
Female, n (%)	41 (66.1)	41 (65.1)
Duration of MG (years), Mean (min, max)	9.9 (1.3, 29.7)	9.2 (1.0, 33.8)
Baseline MG-ADL Score		
Mean (SD)	10.5 (3.06)	9.9 (2.58)
Median	10.0	9.0
Baseline QMG Score		
Mean (SD)	17.3 (5.10)	16.9 (5.56)
Median	17.0	16.0
≥3 Prior Immunosuppressive Therapies* since diagnosis, n (%)	31 (50.0)	34 (54.0)
Number of patients with prior exacerbations since diagnosis, n (%)	46 (74.2)	52 (82.5)
Number of patients with prior MG crisis since diagnosis, n (%)	13 (21.0)	10 (15.9)
Any prior ventilator support since diagnosis, n (%)	15 (24.2)	14 (22.2)
Any prior intubation since diagnosis (MGFA class V), n (%)	11 (17.7)	9 (14.3)

* Immunosuppressant's included, but are not limited to, corticosteroids, azathioprine, mycophenolate, methotrexate , cyclosporine, tacrolimus, or cyclophosphamide.

The primary endpoint for Study ECU-MG-301 was the change from baseline in the MG Activities of Daily Living Profile (MG-ADL – a patient reported outcome measure validated in gMG) total score at Week 26. The primary analysis of the MG-ADL was a Worst-Rank ANCOVA with a mean rank of 56.6 for Soliris and 68.3 for placebo, based on 125 study patients (p=0.0698).

The key secondary endpoint was the change from baseline in the Quantitative MG Scoring System (QMG – a physician reported outcome measure validated in gMG) total score at Week 26. The primary analysis of the QMG was a Worst-Rank ANCOVA with a mean rank of 54.7 for Soliris and 70.7 for placebo, based on 125 study patients (p=0.0129).

Efficacy outcomes for the pre-specified repeated measures analyses of the primary and secondary endpoints are provided in Table 10.

Table 10: ECU-MG-301 Efficacy Outcomes Change from Baseline to Week 26

Efficacy Endpoints: Total score change from baseline at Week 26	Soliris (n=62) (SEM)	Placebo (n=63) (SEM)	Soliris change relative to placebo – LS Mean Difference (95% CI)	p-value (using repeated measures analysis)
MG-ADL	-4.2 (0.49)	-2.3(0.48)	-1.9 (-3.3, -0.6)	0.0058
QMG	-4.6 (0.60)	-1.6 (0.59)	-3.0 (-4.6, -1.3)	0.0006
MGC	-8.1 (0.96)	-4.8 (0.94)	-3.4 (-6.0, -0.7)	0.0134
MG-QoL-15	-12.6 (1.52)	-5.4 (1.49)	-7.2 (-11.5, -3.0)	0.0010

SEM= Standard Error of the Mean CI= Confidence Interval, MGC= Myasthenia Gravis Composite, MG-QoL15= Myasthenia Gravis Qualtiy of Life 15

In Study ECU-MG-301, a clinical responder in the MG-ADL total score was defined as having at least a 3-point improvement. The proportion of clinical responders at Week 26 with no rescue therapy was 59.7% on Soliris compared with 39.7% on placebo (p=0.0229).
In Study ECU-MG-301, a clinical responder in the QMG total score was defined as having at least a 5-point improvement. The proportion of clinical responders at Week 26 with no rescue therapy was 45.2% on Soliris compared with 19% on placebo (p=0.0018).

Table 11 presents an overview of the patients reporting clinical deterioration and patients requiring rescue therapy over the 26 weeks.

Table 11: Clinical deterioration and rescue therapy in ECU-MG-301

Variable	Statistic	Placebo (N=63)	Soliris (N=62)
Total number of patients reporting clinical deterioration	n (%)	15 (23.8)	6 (9.7)
Total number of patients requiring rescue therapy	n (%)	12 (19.0)	6 (9.7)

Of the 125 patients enrolled in ECU-MG-301, 117 patients subsequently were enrolled in a long-term extension study (Study ECU-MG-302), in which all receive Soliris. Patients that were previously treated with Soliris in Study ECU-MG-301 continued to demonstrate a sustained effect of Soliris on all measures (MG-ADL, QMG, MGC and MG-QoL15) over an additional 52 weeks of treatment with Soliris. Figure 1 presents the change from baseline in both MG-ADL (A) and QMG (B) after 26 weeks of treatment in Study ECU-MG-301 and after 52 weeks of treatment in Study ECU-MG-302.

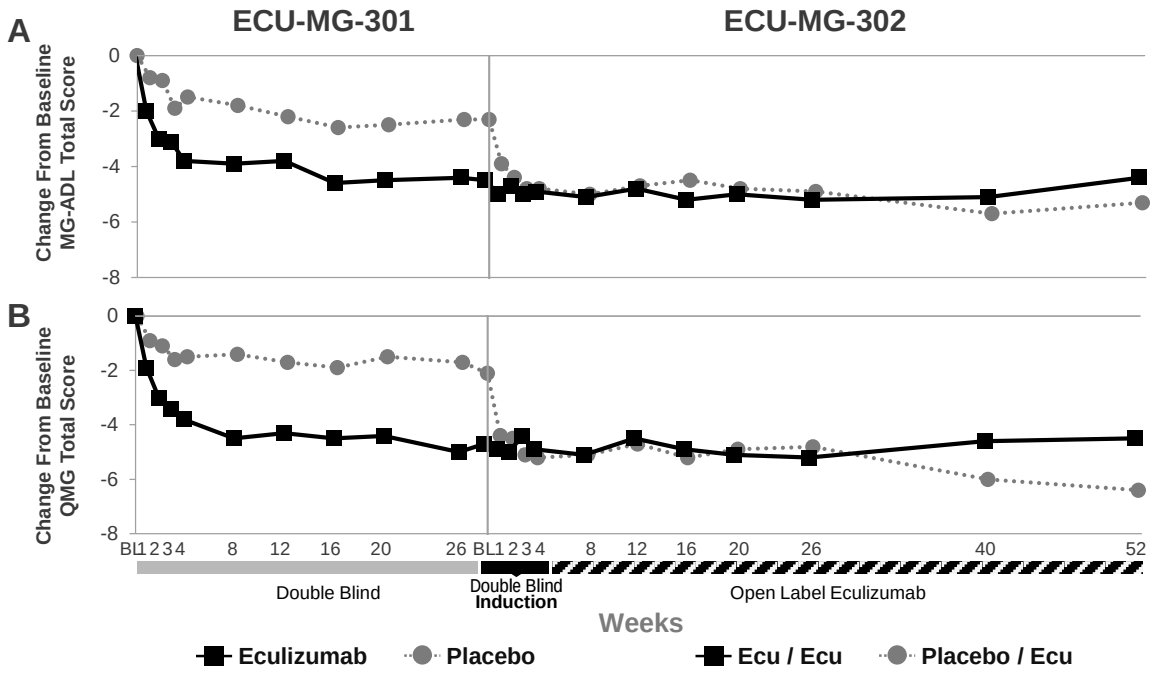

Figure 1: Mean changes from baseline in MG-ADL (1A) and QMG (1B) over Studies ECU-MG-301 and ECU-MG-302

Twenty-two (22) (17.6%) elderly refractory gMG patients (> 65 years of age) were treated with Soliris in the clinical trials. No substantial differences were seen in safety and efficacy related to age.

Paediatric population

Paroxysmal Nocturnal Haemoglobinuria

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

Treatment with eculizumab at the proposed dosing regimen in the paediatric population was associated with a reduction of intravascular haemolysis as measured by serum LDH level. It also resulted in a marked decrease or elimination of blood transfusions, and a trend towards an overall improvement in general function. The efficacy of eculizumab treatment in paediatric PNH patients appears to be consistent with that observed in adult PNH patients enrolled in PNH pivotal Studies (C04-001 and C04-002) (Table 3 and 12).

Table 12: Efficacy Outcomes in Paediatric PNH Study M07-005

		P – Value	
	Mean (SD)	Wilcoxon Signed Rank	Paired t-test
Change from baseline at 12 weeks of LDH Value (U/L)	-771 (914)	0.0156	0.0336
LDH AUC (U/L x Day)	-60,634 (72,916)	0.0156	0.0350
Change from baseline at 12 weeks in Plasma Free Haemoglobin (mg/dL)	-10.3 (21.13)	0.2188	0.1232
Change from baseline Type III RBC clone size (Percent of aberrant cells)	1.80 (358.1)		
Change from baseline at 12 weeks of PedsQL™4.0 Generic Core scale (patients)	10.5 (6.66)	0.1250	0.0256
Change from baseline at 12 weeks of PedsQL™4.0 Generic Core scale (parents)	11.3 (8.5)	0.2500	0.0737
Change from baseline at 12 weeks of PedsQL™ Multidimensional Fatigue (patients)	0.8 (21.39)	0.6250	0.4687
Change from baseline at 12 weeks of PedsQL™ Multidimensional Fatigue (parents)	5.5 (0.71)	0.5000	0.0289

Atypical Haemolytic Uremic Syndrome

A total of 15 paediatric patients (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, 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 < 2 years of age (n=5) and 31 weeks (range 19 to 63 weeks) for children 2 to <12 years of age (n=10).
Overall, the efficacy results for these paediatric patients appeared consistent with what was observed in patients enrolled in aHUS pivotal Studies C08-002 and C08-003 (Table 6). No paediatric patient required new dialysis during treatment with Soliris.

Table 13: Efficacy Results in Paediatric Patients Enrolled in aHUS C09-001r

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

In paediatric patients with shorter duration of current severe clinical thrombotic microangiopathy (TMA) manifestation prior to eculizumab, there was TMA control and improvement of renal function with eculizumab treatment (Table 13).
In paediatric patients with longer duration of current severe clinical TMA manifestation prior to eculizumab, there was TMA control with eculizumab treatment. However, renal function was not changed due to prior irreversible kidney damage (Table 14).

Table 14: Efficacy Outcomes in Paediatric Patients in Study C09-001r according to duration of current severe clinical thrombotic microangiopathy (TMA) manifestation

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

*One patient achieved eGFR improvement after renal transplant

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

In Study C10-003, patients who enrolled in the study were required to have a platelet count < lower limit of normal range (LLN), evidence of haemolysis such as an elevation in serum LDH above the upper limits of normal and serum creatinine level ≥97 percentile for age without the need for chronic dialysis. The median patient age was 6.5 years (range: 5 months to 17 years). Patients enrolled in aHUS C10-003 had an ADAMTS-13 level above 5%. Fifty percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 10 patients received PE/PI prior to eculizumab. Table 15 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in aHUS Study C10-003.

Table 15: Baseline Characteristics of Paediatric and Adolescents Patients Enrolled in aHUS Study C10-003

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

Patients in aHUS C10-003 received Soliris for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients elected to continue on chronic dosing. Reduction in terminal complement activity was observed in all patients after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. The mean (±SD) platelet count increased from 88 ± 42 x10^9/L at baseline to 281 ± 123 x10^9/L by one week; this effect was maintained through 26 weeks (mean platelet count (±SD) at week 26: 293 ± 106 x10^9/L). Renal function, as measured by eGFR, was improved during Soliris therapy. Nine of the 11 patients who required dialysis at baseline no longer required dialysis after Study Day 15 of eculizumab treatment. Responses were similar across all ages from 5 months to 17 years of age. In aHUS C10-003, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

Table 16 summarizes the efficacy results for aHUS C10-003.

Table 16: Efficacy Outcomes in Prospective aHUS Study C10-003

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

Efficacy Parameter	1 month to <12 years (N = 18) At 26-weeks	All Patients (N = 22) At 26-weeks
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 (%)	16 (89)	20 (91)
New Dialysis Event-Free Status, n (%)	18 (100)	22 (100)
95% CI	NA	85;100

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

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

Refractory Generalized Myasthenia Gravis
Soliris has not been evaluated in paediatric patients with refractory gMG.
The European Medicines Agency has deferred the obligation to submit the results of studies with Soliris in one or more subsets of the paediatric population in the treatment of refractory gMG (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pharmacokinetics and Drug Metabolism

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

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

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

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

A second population PK analysis with a standard 1 compartmental model was conducted on the multiple dose PK data from 37 aHUS patients receiving the recommended Soliris regimen in studies C08-002A/B and C08-003A/B. In this model, the clearance of Soliris for a typical aHUS patient

weighing 70 kg was 0.0139 L/hr and the volume of distribution was 5.6 L. The elimination half-life was 297 h (approximately 12.4 days).

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

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

All aHUS patients treated with Soliris when administered as recommended demonstrated rapid and sustained reduction in terminal complement activity. In aHUS patients, pharmacodynamic activity correlates directly with eculizumab serum concentrations and maintenance of trough levels of approximately 50-100 microgram/ml results in essentially complete blockade of terminal complement activity in all aHUS patients.

PK parameters observed in the refractory gMG population are consistent with what has been observed in PNH and aHUS populations.
Pharmacodynamic activity measured by free C5 concentrations of <0.5 ug/mL, is correlated with essentially complete blockade of terminal complement activity in PNH, aHUS, and refractory gMG patients.

Special Populations

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

Paediatric population

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

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

aHUS

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

5.3 Preclinical safety data

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

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

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

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

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

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

No animal studies have been conducted to evaluate the genotoxic and carcinogenic potential of eculizumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

30 months.

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

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.
Soliris vials in the original package may be removed from refrigerated storage **for only one single period of up to 3 days**. At the end of this period the product can be put back in the refrigerator.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

Pack size of one vial.

6.6 Special precautions for disposal and other handling

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

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

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

Transfer the recommended dose to an infusion bag.

Dilute Soliris to a final concentration of 5 mg/ml by addition to the infusion bag using sodium chloride 9 mg/ml (0.9%) solution for injection, sodium chloride 4.5 mg/ml (0.45%) solution for injection, or 5% dextrose in water, as the diluent.
The final volume of a 5 mg/ml diluted solution is 60 ml for 300 mg doses, 120 ml for 600 mg doses, 180 ml for 900 mg doses and 240 ml for 1,200 mg doses. The solution should be clear and colourless.

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

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

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

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

7. MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
1-15, avenue Edouard Belin
92500 Rueil-Malmaison
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/393/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 20 June 2007
Date of latest renewal : 18 June 2012

10. DATE OF REVISION OF THE TEXT

Date: 14/12/2017

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/ .

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Lonza Biologics, plc.
228 Bath Road
Slough
Berkshire SL1 4DX
United Kingdom

Alexion Rhode Island Manufacturing Facility (ARIMF)
100 Technology Way
Smithfield, Rhode Island 02917
U.S.A.

Lonza Biologics Tuas Pte Ltd.
35 Tuas South Avenue 6
Singapore 637377

Lonza Biologics Porriño, S.L.
C/ La Relba, s/n.
Porriño
Pontevedra 36400
Spain

Name and address of the manufacturers responsible for batch release

Almac Pharma Services
22 Seagoe Industrial Estate
Craigavon BT63 5QD
United Kingdom

Patheon Italia S.p.A
Viale G. B. Stucchi, 110
20900 Monza (MB)
Italy

Alexion Pharma International
Operations Unlimited Company
College Business and Technology Park
Blanchardstown
Dublin 15
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Periodic Safety Update Reports
The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk Management Plan (RMP)
The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation, and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The MAH shall agree the details of a controlled drug distribution system and educational material including a patient safety card with each National Competent Authority and must implement such programmes nationally to ensure that:

1. All healthcare practitioners who may prescribe eculizumab receive the appropriate educational material.

2. All patients being treated with eculizumab receive a patient safety card.

3. Drug distribution will only be possible after written confirmation that the patient received or will receive meningococcal vaccination and/or antibiotic prophylaxis.

4. Vaccination reminders are sent to the prescribers.

The educational material should be agreed with the National Competent Authority and should contain the following:

- Summary of product characteristics
- Physician's guides to prescribing
- Patient's/carer's information brochures
- Patient safety card

The physician's guides to prescribing should be indication specific and contain the following key messages:

- Treatment with eculizumab increases the risk of severe infection and sepsis, especially of *Neisseria meningitidis.*
- All patients must be monitored for signs of meningitis.
- The need for patients to be vaccinated against Neisseria meningitidis two weeks prior to receiving eculizumab and/or to receive antibiotic prophylaxis.

- The requirement to vaccinate children against pneumococcus and *Haemophilus influenzae* before eculizumab treatment.
- There is an important risk of Aspergillus infection in patients treated with eculizumab. The healthcare professionals should be advised to look for risk factors and signs and symptoms of Aspergillus infection. Practical advice should be included to mitigate the risk.
- The risk of infusion reactions including anaphylaxis and advice on post-infusion monitoring.
- The risk of developing antibodies to eculizumab.
- Risk of serious haemolysis following eculizumab discontinuation and postponement of administration, its criteria, the required post-treatment monitoring and its proposed management (PNH only).
- Risk of severe thrombotic microangiopathic complications following eculizumab discontinuation and postponement of administration, its signs, symptoms, monitoring and management (aHUS only).
- Risk of substantial disease exacerbation or relapse following eculizumab discontinuation (refractory gMG only)
- The need to explain to and ensure understanding of by patients/carers:
    - the risks of treatment with eculizumab
    - the signs and symptoms of sepsis/severe infection and what action to take
    - the patient's/carer's guides and their contents
    - the need to carry the patient safety card and to tell any healthcare practitioner that he/she is receiving treatment with eculizumab
    - the requirement for vaccinations/antibiotic prophylaxis
    - the enrolment in the registries
- Details of the PNH and aHUS registries and how to enter patients.

The patient's/carer's guides should be indication specific and contain the following key messages:

- Treatment with eculizumab increases the risk of severe infection, especially *Neisseria meningitidis.*
- Signs and symptoms of severe infection and the need to obtain urgent medical care.
- The patient safety card and the need to carry it on their person and tell any treating healthcare professional that they are being treated with eculizumab.
- The importance of meningococcal vaccination prior to treatment with eculizumab and/or to receive antibiotic prophylaxis.
- The need for children to be vaccinated against pneumococcus and *Haemophilus influenzae* before eculizumab treatment.
- The risk of infusion reactions with eculizumab, including anaphylaxis, and the need for clinical monitoring post-infusion.
- Risk of severe thrombotic microangiopathic complications (in aHUS) following discontinuation/postponement of eculizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations.
- Risk of serious haemolysis (in PNH) following discontinuation/postponement of eculizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations.
- Risk of substantial disease exacerbation or relapse (in refractory gMG) following discontinuation/postponement of eculizumab administrations and recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations.
- Enrolment in the PNH and aHUS registries.

The patient safety card should contain:

- Signs and symptoms of infection and sepsis.
- Warning to seek immediate medical care if above are present.
- Statement that the patient is receiving eculizumab.
- Contact details where a health care practitioner can receive further information.

The MAH shall send annually to prescribers or pharmacists who prescribe/dispense eculizumab, a reminder in order that prescriber/pharmacist checks if a (re)-vaccination against Neisseria meningitidis is needed for his/her patients on eculizumab.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton Label

1. NAME OF THE MEDICINAL PRODUCT

Soliris 300 mg concentrate for solution for infusion
Eculizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of 30 ml contains 300 mg of eculizumab (10mg/ml)

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

After dilution, the final concentration of the solution to be infused is 5 mg/ml.

3. LIST OF EXCIPIENTS

Sodium as chloride, phosphate dibasic, phosphate monobasic, polysorbate 80 and water for injections.

See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial of 30 ml (10 mg/ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.
Must be diluted before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After dilution, the medicinal product should be used within 24 hours.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Alexion Europe SAS
1-15, avenue Edouard Belin
92500 Rueil-Malmaison
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/393/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Single use Type I glass vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Soliris 300 mg concentrate for solution for infusion
Eculizumab
For intravenous use

2. METHOD OF ADMINISTRATION

To be diluted before use.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 ml (10 mg/ml)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Soliris 300 mg concentrate for solution for infusion
Eculizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Soliris is and what it is used for

What is Soliris
Soliris contains the active substance eculizumab and it belongs to a class of medicines called monoclonal antibodies. Eculizumab binds to and inhibits a specific protein in the body that causes inflammation and so prevents your body's systems from attacking and destroying vulnerable blood cells.

What is Soliris used for
Paroxysmal Nocturnal Haemoglobinuria
Soliris is used to treat adults and children patients with a certain type of disease affecting the blood system called Paroxysmal Nocturnal Haemoglobinuria (PNH). In patients with PNH, their red blood cells can be destroyed which can lead to low blood counts (anaemia), tiredness, difficulty in functioning, pain, dark urine, shortness of breath, and blood clots. Eculizumab can block the body's inflammatory response, and its ability to attack and destroy its own vulnerable PNH blood cells.

Atypical Haemolytic Uremic Syndrome
Soliris is also used to treat adults and children patients with a certain type of disease affecting the blood system and kidney called atypical Haemolytic Uremic Syndrome (aHUS). In patients with aHUS, their kidney and blood cells, including platelets, can be inflamed which can lead to low blood counts (thrombocytopenia and anaemia), reduced or lost kidney function, blood clots, tiredness and difficulty in functioning. Eculizumab can block the body's inflammatory response, and its ability to attack and destroy its own vulnerable blood and kidney cells.

Refractory Generalized Myasthenia Gravis
Soliris is also used to treat adult patients with a certain type of disease affecting the muscles and called generalized Myasthenia Gravis (gMG). In patients with gMG, their muscles can be attacked and damaged by the immune system which can lead to profound muscle weakness, impaired mobility, shortness of breath, extreme fatigue, risk for aspiration, and markedly impaired activities of daily living. Soliris can block the body's inflammatory response, and its ability to attack and destroy its own muscles to improve muscle contraction, thereby reducing symptoms of the disease and impact of the disease on the activities of daily living. Soliris is specifically indicated for patients who remain symptomatic despite treatment with other existing MG therapies.

2. What you need to know before you use Soliris

Do not use Soliris

- If you are allergic to eculizumab, proteins derived from mouse products, other monoclonal antibodies, or any of the other ingredients of this medicine (listed in section 6).
- If you have not been vaccinated against meningococcal infection unless you take antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated .
- If you have a meningitis infection.

Warnings and precautions

Meningitis alert
Soliris treatment may reduce your natural resistance to infections, especially against certain organisms that cause meningitis (infection of the linings of the brain).

Consult your doctor before you take Soliris to be sure that you receive vaccination against *Neisseria meningitidis*, an organism that causes meningitis, at least 2 weeks before beginning therapy, or that you take antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated. Ensure that your current meningitis vaccination is up to date. You should also be aware that vaccination may not prevent this type of infection. In accordance with national recommendations, your doctor might consider that you need supplementary measures to prevent infection.

Meningitis symptoms
Because of the importance of rapidly identifying and treating certain types of infection in patients who receive Soliris, you will be provided a card to carry with you, listing specific trigger symptoms. This card is named: “Patient Safety Card”.

If you experience any of the following symptoms, you should immediately inform your doctor:
- headache with nausea or vomiting
- headache with a stiff neck or back
- fever
- rash
- confusion
- severe muscle aches combined with flu-like symptoms
- sensitivity to light

Treatment for meningitis while travelling
If you are travelling in a remote region where you are unable to contact your doctor or in which you find yourself temporarily unable to receive medical treatment, your doctor can make arrangements to issue, as a preventive measure, a prescription for an antibiotic to counter *Neisseria meningitidis* that you keep with you. If you experience any of the symptoms amongst those cited above, you should take the antibiotics as prescribed. You should bear in mind that you should see a doctor as soon as possible, even if you feel better after having taken the antibiotics.

Infections
Before starting Soliris, inform your doctor if you have any infections.

Allergic reactions
Soliris contains a protein and proteins can cause allergic reactions in some people.

Children and adolescents
Patients less than 18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections

Older people
There are no special precautions needed for the treatment of patients aged from 65 years and over.

Other medicines and Soliris
Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines.

Pregnancy, breast-feeding, and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Women of childbearing potential
The use of effective contraception during treatment and up to 5 months after treatment should be considered in women who are able to get pregnant.

Pregnancy/ Breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines
Soliris has no or negligible influence on the ability to drive and use machines.

Soliris contains sodium
This medicinal product contains 115 mg sodium per vial. You should take into consideration if you are on a controlled sodium diet.

3. How to use Soliris

At least 2 weeks before you start treatment with Soliris, your doctor will administer a vaccine against meningitis if it was not previously administered or if your vaccination is outdated. If your child is below the age of vaccination or if you are not vaccinated at least 2 weeks before you start treatment with Soliris, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated.
Your doctor will administer a vaccine to your child aged less than 18 years against *Haemophilus influenzae* and pneumococcal infections according to the national vaccination recommendations for each age group.

Instructions for proper use
The treatment will be given by your doctor or other health care provider by infusing a dilution of the Soliris vial from a drip bag through a tube directly into one of your veins. It is recommended that the beginning of your treatments, called the initial phase, will extend over 4 weeks, followed by a maintenance phase.

<u>If you use this medicine to treat PNH</u>
For adults:
- Initial Phase:
  Every week for the first four weeks, your doctor will administer an intravenous infusion of diluted Soliris**.** Each infusion will consist of a dose of 600 mg (2 vials of 30 ml) and will take 25 – 45 minutes.

- Maintenance Phase:
    - In the fifth week, your doctor will administer an intravenous infusion of diluted Soliris at a dose of 900 mg (3 vials of 30 ml) over a 25 – 45 minute period.
    - After the fifth week, your doctor will administer 900 mg of diluted Soliris every two weeks as a long-term treatment.

If you use this medicine to treat aHUS or refractory gMG
For adults:

- Initial Phase:
  Every week for the first four weeks, your doctor will administer an intravenous infusion of diluted Soliris**.** Each infusion will consist of a dose of 900 mg (3 vials of 30 ml) and will take 25 – 45 minutes.

- Maintenance Phase:
    - In the fifth week, your doctor will administer an intravenous infusion of diluted Soliris at a dose of 1,200 mg (4 vials of 30 ml) over a 25 – 45 minute period.
    - After the fifth week, your doctor will administer 1,200 mg of diluted Soliris every two weeks as a long-term treatment.

Children and adolescents with PNH or aHUS and who are 40 kg weight and over are treated with the adult dosing.

Children and adolescents with PNH or aHUS and who are under 40 kg weight require a lower dose based on how much they weigh. Your doctor will calculate this.

For children and adolescents with PNH and aHUS aged less than 18 years:

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

Subjects who undergo plasma exchange may receive additional doses of Soliris.

Following each infusion, you will be monitored for about one hour. Your doctor's instructions should be carefully observed.

If you receive more Soliris than you should
If you suspect that you have been accidentally administered a higher dose of Soliris than prescribed, please contact your doctor for advice.

If you forget an appointment to receive Soliris
If you forget an appointment, please contact your doctor immediately for advice and see section below "If you stop using Soliris".

If you stop using Soliris for PNH
Interrupting or ending treatment with Soliris may cause your PNH symptoms to come back more severely soon. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely for at least 8 weeks.

The risks of stopping Soliris include an increase in the destruction of your red blood cells, which may cause:
- A significant fall in your red blood cell counts (anaemia),
- Confusion or change in how alert you are,
- Chest pain, or angina,
- An increase in your serum creatinine level (problems with your kidneys), or

- Thrombosis (blood clotting).

If you have any of these symptoms, contact your doctor.

If you stop using Soliris for aHUS
Interrupting or ending treatment with Soliris may cause your aHUS symptoms to come back. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely.

The risks of stopping Soliris include an increase in the inflammation of your platelets, which may cause:
- A significant fall in your platelets (thrombocytopenia),
- A significant rise in destruction of your red blood cells,
- Decreased urination (problems with your kidneys),
- An increase in your serum creatinine level (problems with your kidneys),
- Confusion or change in how alert you are,
- Chest pain, or angina,
- Shortness of breath, or
- Thrombosis (blood clotting).

If you have any of these symptoms, contact your doctor.

If you stop using Soliris for refractory gMG
Interrupting or stopping treatment with Soliris may cause your gMG symptoms to come back. Please speak to your doctor before stopping Soliris. Your doctor will discuss the possible side effects and risks with you. Your doctor will also want to monitor you closely.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss the possible side effects with you and explain the risks and benefits of Soliris with you prior to treatment.
The most serious side effect was meningococcal sepsis.
If you experience any of the meningitis symptoms (see section 2 Meningitis alert), you should immediately inform your doctor.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

Very common: may affect more than 1 in 10 people: headache.

Common: may affect up to 1 in 10 people:
- infection of the lung (pneumonia), common cold (nasopharyngitis), infection of the urinary system (urinary tract infection),
- low white blood cell count (leukopenia), reduction in red blood cells which can make the skin pale and cause weakness or breathlessness
- inability to sleep
- dizziness, taste disorders (dysgeusia), shaking
- high blood pressure
- upper respiratory tract infection, cough, throat pain (oropharyngeal pain),
- diarrhea, vomiting, nausea, abdominal pain, rash, hair loss (alopecia), itchy skin (pruritus)
- pain in the limbs or joints (arms and legs)
- fever (pyrexia), chills, feeling tired (fatigue), influenza like illness

Uncommon: may affect up to 1 in 100 people:
- severe infection (meningococcal infection), sepsis, septic shock, viral infection, bronchitis, cold sores (herpes simplex), lower respiratory tract infection, stomach flu (gastrointestinal infection), cystitis
- infection, fungal infection, collection of pus (abscess), type of infection of the skin (cellulitis), influenza, sinusitis, tooth infection
- relatively few platelets in blood (thrombocytopenia), low level of lymphocytes a specific type of white blood cells (lymphopenia), feeling your heartbeat
- serious allergic reaction which causes difficulty in breathing or dizziness (anaphylactic reaction), hypersensitivity
- loss of appetite
- depression, anxiety, mood swings
- tingling in part of the body (paresthesia)
- vision blurred
- ringing in the ears, vertigo
- sudden and rapid development of extremely high blood pressure, low blood pressure, hot flush, vein disorder
- dyspnoea (difficulty breathing), nose bleed, stuffy nose (nasal congestion), throat irritation, runny nose (rhinorrhoea)
- inflammation of the peritoneum (the tissue that lines most of the organs of the abdomen), constipation, stomach discomfort after meals (dyspepsia), abdominal distension
- hives, redness of the skin, dry skin, red or purple spots under the skin, increased sweating
- muscle cramp, muscle aches, back and neck pain, bone pain, joint swelling
- kidney disorder, difficulties or pain when urinating (dysuria)
- spontaneous penile erection
- swelling (edema), chest discomfort, feeling of weakness (asthenia), chest pain, infusion site pain
- increase of liver enzymes, decrease of the proportion of blood volume that is occupied by red blood cells, decrease in the protein in red blood cells that carries oxygen

Rare: may affect up to 1 in 1,000 people:
- infection by fungi (Aspergillus infection), infection of the joint (arthritis bacterial), *Haemophilus influenzae* infection, gum infection, impetigo, bacterial sexual transmitted disease
- skin tumor (melanoma), bone marrow disorder
- destruction of red blood cells (haemolysis), clumping of cells, abnormal clotting factor, abnormal blood clotting,
- disease with thyroid overactivity (Basedow's disease)
- sleep disorder, abnormal dreams
- fainting
- irritation of eye
- bruise
- unusual backflow of food from stomach, gum pain
- yellowing of the skin and/or eyes (jaundice)
- inflammation of the skin, skin color disorder
- spasm of mouth muscle
- blood in urine
- menstrual disorder
- abnormal leakage of the infused drug out of the vein, infusion site abnormal sensation, feeling hot
- infusion related reaction

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Soliris

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.
Store in a refrigerator (2°C – 8°C).
Do not freeze.
Soliris vials in the original package may be removed from refrigerated storage **for only one single period of up to 3 days**. At the end of this period the product can be put back in the refrigerator.
Store in the original package in order to protect from light.
After dilution, the product should be used within 24 hours.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Soliris contains

– The active substance is eculizumab (300 mg/30 ml in a vial corresponding to 10 mg/ml).

– The other ingredients are:
  - sodium phosphate monobasic
  - sodium phosphate dibasic
  - sodium chloride
  - polysorbate 80 (vegetable origin)

  Solvent: water for injections

What Soliris looks like and contents of the pack
Soliris is presented as a concentrate for solution for infusion (30 ml in a vial – pack size of 1).
Soliris is a clear and colorless solution.

Marketing Authorisation Holder
Alexion Europe SAS
1-15, avenue Edouard Belin
92500 Rueil-Malmaison
France

Manufacturer
Almac Pharma Services
22 Seagoe Industrial Estate
Craigavon BT63 5QD
United Kingdom

Patheon Italia S.p.A
Viale G. B. Stucchi, 110
20900 Monza (MB)
Italy

Alexion Pharma International Operations
Unlimited Company
College Business and Technology Park
Blanchardstown
Dublin 15
Ireland

This leaflet was last revised in December 2017.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/. There are also links to other websites about rare diseases and treatments.

Instructions for Use for Healthcare Professionals
Handling Soliris

The following information is intended for medical or healthcare professionals only:

1- How is Soliris supplied?
Each vial of Soliris contains 300 mg of active ingredient in 30 ml of product solution.

2- Before Administration
Reconstitution and dilution should be performed in accordance with good practices rules, particularly for the respect of asepsis.
Soliris should be prepared for administration by a qualified healthcare professional using aseptic technique.

- Inspect visually Soliris solution for particulate matter and discolouration.
- Withdraw the required amount of Soliris from the vial(s) using a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute Soliris to a final concentration of 5 mg/ml (initial concentration divided by 2) by adding the appropriate amount of diluent to the infusion bag. For 300 mg doses, use 30 ml of Soliris (10 mg/ml) and add 30 ml of diluent. For 600 mg doses, use 60 ml of Soliris and add 60 ml of diluent. For 900 mg doses, use 90 ml of Soliris and add 90 ml of diluent. For 1,200 mg doses, use 120 ml of Soliris and add 120 ml of diluent. The final volume of a 5 mg/ml diluted Soliris solution is 60 ml for 300 mg doses, 120 ml for 600 mg doses, 180 ml for 900 mg doses or 240 ml for 1,200 mg doses.
- Diluents are Sodium chloride 9 mg/ml (0.9%) solution for injection, Sodium chloride 4.5 mg/ml (0.45%) solution for injection or 5% dextrose in Water.
- Gently agitate the infusion bag containing the diluted Soliris solution to ensure thorough mixing of the medicinal product and diluent.
- The diluted solution should be allowed to warm to room temperature [18°C – 25°C] prior to administration by exposure to ambient air.
- The diluted solution must not be heated in a microwave or with any heat source other than the prevailing room temperature.
- Discard any unused portion left in a vial as the medicinal product contains no preservatives.
- Diluted solution of Soliris may be stored at 2°C – 8°C for up to 24 hours prior to administration.

3- Administration

- Do not administer Soliris as an intravenous push or bolus injection.
- Soliris should only be administered via intravenous infusion.
- The diluted solution of Soliris should be administered by intravenous infusion over 25 to 45 minutes in adults and 1-4 hours in paediatric patients 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.

The patient should be monitored for one hour following infusion. If an adverse event occurs during the administration of Soliris, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time may not exceed two hours in adults and adolescents and four hours in children aged less than 12.

4- Special Handling and Storage
Store in a refrigerator (2°C – 8°C). Do not freeze. Store in the original package in order to protect from light. Soliris vials in the original package may be removed from refrigerated storage **for only one single period of up to 3 days**. At the end of this period the product can be put back in the refrigerator.
Do not use this medicine after the expiry date which is stated on the carton after ‘EXP’. The expiry date refers to the last day of that month.