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EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for SOLIRIS® (eculizumab)

The content of this EU RMP has been reviewed and approved by the Marketing Authorisation Holder's QPPV or deputy QPPV, as delegated by the QPPV in the EU.

SOLIRIS® is a trademark of the AstraZeneca group of companies.

Administrative information

Rationale for submitting an updated RMP:

This RMP update is submitted with the revised additional risk minimisation measures for SOLIRIS.

Summary of significant changes in this RMP

Part II SVII and SVIII

"Serious haemolysis after drug discontinuation in PNH patients" and "Immunogenicity" previously classified as important potential risks, and "Aspergillus Infection" previously classified as important identified risk are proposed to be removed from the list of safety concerns, based on the rationale provided in Section 2.7.2 of the RMP.

Part III

A completed category 3 PASS, aHUS registry (M11-001), was removed from the pharmacovigilance plan in Sections 3.2 and 3.3.

Part V

The routine risk minimisation measures were aligned with the proposed changes to the list of safety concerns in Part II of the RMP.

The revised additional risk minimisation measures in place for SOLIRIS were presented in Section 5.2.

Section 5.3 was revised in line with the changes made in Sections 3.2 and 3.3 and Sections 5.1 and 5.2 of the RMP.

Part VI

All changes made in the body of document were reflected in the Summary of the RMP, as applicable.

Part VII

Annex 2 was revised to reflect on the completed PASS aHUS Registry (M11-001).

The link to aHUS registry protocol was removed from Annex 3, since this PASS was completed.

The approved key messages for the revised additional risk minimisation measures were provided in Annex 6 to reflect on the changes made in the body of the document in Section 5.2.

Other RMP versions under evaluation	**Version number**: Not applicable. **Submitted**: Not applicable. **Procedure number**: Not applicable.
Details of currently approved RMP	**Version number**: 20.3 **Approved with procedure**: EMEA/H/C/000791/II/0126 **Date of approval:** 22 June 2023

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
AChR	Acetylcholine Receptor
ADA	Anti-drug Antibodies
aHUS	Atypical Haemolytic Uremic Syndrome
AQP-4	Aquaporin-4
AQP4Ab	Aquaporin-4 Antibody
ATC	Anatomical Therapeutic Chemical classification system
AZA	Azathioprine
C3	Complement Component 3
C5	Complement Component 5
CFH	Complement Factor H
CFI	Complement Factor I
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
D-HUS	Diarrhoea-associated Haemolytic Uremic Syndrome
DNA	Deoxyribonucleic Acid
EEA	European Economic Area
EPAR	European Public Assessment Report
ESRD	End-stage Renal Disease
EU	European Union
gMG	Generalised Myasthenia Gravis
GPI	Glycosylphosphatidylinositol
HCP	Healthcare Professional
HUS	Haemolytic Uremic Syndrome
IBD	International Birth Date
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
INN	International Non-proprietary Name
LETM	Longitudinally Extensive Transverse Myelitis
MAH	Marketing Authorisation Holder
MCP	Membrane Cofactor Protein
MG	Myasthenia Gravis

Abbreviation/ Special term	Definition/Explanation
MMF	Mycophenolate Mofetil
MuSK	Muscle-specific Receptor Tyrosine Kinase
NMO	Neuromyelitis Optica
NMOSD	Neuromyelitis Optica Spectrum Disorder
PIGA	X-linked Phosphatidylinositol Glycan A Gene
PL	Package Leaflet
PNH	Paroxysmal nocturnal Haemoglobinuria
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
TMA	Thrombotic Microangiopathy
UK	United Kingdom
US	United States

1 PART I: PRODUCT(S) OVERVIEW

Table 1-1 Product(s) overview

Active substance(s) (INN or common name)	Eculizumab
Pharmacotherapeutic group(s) (ATC code)	L04AA25
Marketing Authorisation Holder	Alexion Europe SAS
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	SOLIRIS
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** SOLIRIS (eculizumab) is a recombinant humanised monoclonal IgG2/4κ antibody produced by murine myeloma cell culture and purified by standard bioprocess technology. Eculizumab contains human constant regions from human IgG_2 and IgG_4 sequences and murine complementarity-determining regions grafted onto the human framework light- and heavy-chain variable regions. Additionally, human IgG_2 and IgG_4 heavy chain sequences were combined to form a hybrid constant region that is unable to bind Fc receptors or to activate the complement cascade. Eculizumab 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.
	Summary of mode of action: Eculizumab inhibits C5 cleavage to C5a and C5b, preventing the generation of the terminal complement complex C5b-9. The affinity of eculizumab for human C5 is extremely high with a dissociation constant of 120 pM. Eculizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.
	Important information about its composition: Eculizumab is a humanised monoclonal antibody produced in the NS0 cell line by recombinant DNA technology.
Hyperlink to the Product Information	SOLIRIS, Product Information

Table 1-1 Product(s) overview

Indication(s) in the EEA	**Current:** 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. • Atypical haemolytic uremic syndrome (aHUS). • Refractory generalised myasthenia gravis (gMG) in patients aged 6 years of age and above who are anti-AChR antibody-positive. SOLIRIS is indicated in adults for the treatment of: • Neuromyelitis optica spectrum disorder (NMOSD) in patients who are anti-aquaporin-4 (AQP4) antibody-positive.
	Proposed: Not applicable.
Dosage in the EEA	**Current:** **Adult patients (PNH, aHUS, refractory gMG, NMOSD):** 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. In atypical Haemolytic Uremic Syndrome (aHUS), refractory generalised Myasthenia Gravis (gMG) and Neuromyelitis Optica Spectrum Disorder (NMOSD): The aHUS, refractory gMG and NMOSD 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

Table 1-1 Product(s) overview

<table>
<tr><td></td><td>via a 25-45-minute intravenous infusion every 14 ± 2 days.
Paediatric patients (PNH, aHUS, or refractory gMG):
Paediatric PNH, aHUS, or refractory gMG patients with body weight ≥ 40 kg are treated with the adult dosing recommendations.
In paediatric PNH, aHUS, or refractory gMG patients with body weight below 40 kg, the SOLIRIS dosing regimen consists of:
<table>
<tr><th>Patient body weight</th><th>Initial phase</th><th>Maintenance phase</th></tr>
<tr><td>30 to <40 kg</td><td>600 mg weekly for the first 2 weeks</td><td>900 mg at week 3; then 900 mg every 2 weeks</td></tr>
<tr><td>20 to <30 kg</td><td>600 mg weekly for the first 2 weeks</td><td>600 mg at week 3; then 600 mg every 2 weeks</td></tr>
<tr><td>10 to <20 kg</td><td>600 mg single dose at week 1</td><td>300 mg at week 2; then 300 mg every 2 weeks</td></tr>
<tr><td>5 to <10 kg</td><td>300 mg single dose at week 1</td><td>300 mg at week 2; then 300 mg every 3 weeks</td></tr>
</table>
Proposed:
Not applicable.</td></tr>
<tr><td>Pharmaceutical form(s) and strengths in the EEA</td><td>Current:
Concentrate for solution for infusion
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.
Proposed:
Not applicable.</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

AChR, acetylcholine receptor; ATC, anatomical therapeutic chemical classification system; C5, complement component 5; DNA, deoxyribonucleic acid; EEA, European Economic Area; EU, European Union; Ig, immunoglobulin; INN, international nonproprietary name; RMP, risk management plan.

2 PART II: SAFETY SPECIFICATION

2.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

2.1.1 Paroxysmal nocturnal haemoglobinuria

Incidence and prevalence:

Epidemiologic studies of the occurrence of paroxysmal nocturnal haemoglobinuria (PNH) are scarce. Incidence of PNH in the European Union (EU) has been reported to range from 0.08 to 0.57 per 100,000 person-years (Hansen et al 2020, Jalbert et al 2019). The Danish National Patient Register provided the lowest incidence estimate of 0.08 per 100,000 persons from 2008 to 2016 (Hansen et al 2020). A study from Spain estimated annual incidence at 0.25 per 100,000 person-years utilising a case definition of a laboratory assessment with glycosylphosphatidylinositol (GPI)-deficient cells in ≥ 2 cell lineages at frequencies of > 0.01% of all leukocytes (Morado et al 2017). A regional study of PNH patients diagnosed by flow cytometry for GPI-linked antigens in England reported an annual incidence of 0.35 per 100,000 person-years from 2004 to 2018 (Richards et al 2021).

Prevalence of PNH has been reported to range from 1.04 to 3.81 per 100,000 persons (Hansen et al 2020, Richards et al 2021).

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

PNH can occur at any age, although it is diagnosed most often in the fourth or fifth decade of life (Füreder et al 2020, Lee et al 2013, Schrezenmeier et al 2020, Villegas et al 2017, Yu et al 2016). PNH is considered rare in children although it may manifest in some patients during teenage years (Hill et al 2017). In general, there is a slight female preponderance in PNH, as noted in several registries (Füreder et al 2020, Socie et al 2016, Villegas et al 2017).

In an analysis of 4,439 patients enrolled in the International PNH registry as of July 2017, 53% were female and median age at diagnosis was 35.5 years (Schrezenmeier et al 2020). Overall, 67.9% of patients were from Europe, 14.4% from the US and 17.7% from the rest of the world, including Asia. In this registry, 78.4% of participants were White, 16.3% were Asian, 3% were Black and the remaining 2.3% were another race or unspecified (Schrezenmeier et al 2020). A separate analysis of this registry, which evaluated Asian and non-Asian patients who were not eculizumab-treated at baseline and who had ≥ 1% PNH clone size, found no statistical difference in age, sex or disease duration between Asian and non-Asian patients (Sakurai et al 2019).

Risk factors

Although PNH has a genetic basis, it is not a heritable condition as it is a somatic mutation of the X-linked phosphatidylinositol glycan A gene (*PIGA*) gene that occurs randomly (Sahin et al 2015). Patients who develop PNH often have some bone marrow dysfunction, such as aplastic anaemia or myelodysplastic syndrome, prior to or concurrently at time of PNH diagnosis (Parker 2012, Rachidi et al 2010). The leading theory suggests that many healthy individuals have some GPI-deficient haematopoietic stem cells, which generally do not preferentially replicate. However, some event, enabling GPI-deficient cells to expand in the presence of bone marrow dysfunction, is needed to induce PNH (Parker 2012, Rachidi et al 2010, Sahin et al 2015).

The main existing treatment options:

Treatment of PNH consists primarily of anti-complement therapies, eculizumab and ravulizumab. Eculizumab, a monoclonal antibody that specifically binds to the complement component 5 (C5) with high affinity, inhibits terminal complement-mediated intravascular haemolysis in PNH patients. More recently, ravulizumab was designed to provide extended duration of terminal complement inhibition, while retaining the safety, efficacy, and low immunogenicity associated with eculizumab (Sheridan et al 2018). Additionally, a complement component 3 (C3) inhibitor pegcetacoplan was approved for treatment of PNH patients who are anaemic after treatment with a C5 inhibitor for at least 3 months.

Prior to the introduction of eculizumab, ravulizumab and most recently of pegcetacoplan, the treatment of PNH was mainly supportive, aiming to control the clinical manifestations of the disease (management of haemolysis, anaemia, thrombophilia, and bone marrow failure). This supportive treatment included blood transfusion, administration of erythropoiesis-stimulating agents, corticosteroids, or anabolic steroids, iron therapy, thrombosis prophylaxis, and thrombolytic therapy (Al-Ani et al 2016).

The only available curative approach for PNH is allogeneic haematopoietic stem cell transplantation. However, allogeneic haematopoietic stem cell transplantation is associated with high mortality and morbidity. Moreover, because of the high effectiveness of eculizumab, stem cell transplantation is only considered for cases of severe marrow failure (Al-Ani et al 2016).

Natural history of the indicated condition in the (untreated) population, including mortality and morbidity:

PNH is a chronic haematological disorder characterised by episodes of haemolysis and other important clinical manifestations including thrombosis, bone marrow failure and evolution to myelodysplastic syndrome (Hill et al 2017). Other serious clinical symptoms lead to poor quality of life in PNH, including anaemia, kidney disease, fatigue, and smooth muscle

dystonia (Hill et al 2017). Specific to patients experiencing clinically evident extravascular haemolysis, an additional complication includes iron overload as the result of eculizumab and ravulizumab blocking intravascular haemolysis and subsequently preventing further urinary iron loss (Risitano et al 2019, Röth et al 2011).

Disease burden was high in an analysis of patients enrolled in the International PNH Registry, with 55.8% reporting haemolysis and 42.8% with an impaired estimated glomerular filtration rate at baseline (defined as the date of enrolment for never treated patients and date of eculizumab initiation for patients ever treated with eculizumab). Further, 63% of patients had a history of bone marrow failure and 18.8% had a history of a major adverse vascular event (Schrezenmeier et al 2020). In this registry, commonly reported PNH symptoms included: fatigue (80.9%), dyspnoea (45.3%), haemoglobinuria (45.0%), abdominal pain (35.2%), dysphagia (16.5%), and erectile dysfunction (24.2% of males) (Schrezenmeier et al 2020).

The survival experience of patients with PNH has improved over time though among untreated patients, mortality remains higher as compared to the general population (Hill et al 2017, Jang et al 2016, Kelly et al 2011). Among those patients treated with eculizumab, the survival experience of patients has been demonstrated to be similar to a matched general population (Füreder et al 2020, Kelly et al 2011).

Thromboembolism is generally considered the most common cause of mortality in PNH patients, accounting for approximately 40% to 67% of deaths with a known cause (Devos et al 2018, Heitlinger 2013, Hill et al 2013).

Important co-morbidities:

- Bone marrow abnormalities

2.1.2 Atypical haemolytic uraemic syndrome

Incidence and prevalence:

Several studies suggest that the proportion of haemolytic uraemic syndrome (HUS) that can be considered atypical HUS (aHUS) is roughly 10%. In a prospective national study of paediatric HUS, the Swiss Paediatric Surveillance Unit found 114 cases of HUS between 1997 and 2003, of which 6 (5%) were considered aHUS (defined as HUS in the absence of *Escherichia coli*) and an additional 6 were due to *Streptococcus pneumoniae*, for a total of 5-10% aHUS, depending on case definition (Schifferli et al 2010). A similar percentage was noted in patients screened for participation in the SYNSORB Pk trial for the treatment of HUS: among 247 paediatric patients screened between 1997 and 2001, 27 (11%) were found to have aHUS (Constantinescu et al 2004). Between 2003 and 2012, the Northern Italian HUS

network identified 101 cases of paediatric HUS, of which 12% were considered aHUS (Ardissino et al 2016).

Slightly higher proportions of aHUS were found in other studies. A retrospective hospital record review in Norway conducted between 1999 and 2008 identified 47 paediatric cases of HUS, of which 9 (19%) were considered to be aHUS (defined as diarrhoea-associated HUS [D-HUS]) (Jenssen et al 2014). A review of 22 paediatric HUS cases in Italy found that 40% were considered to have aHUS (defined as D-HUS) and were not associated with an *E coli* infection (Micheletti et al 2010).

The incidence of aHUS in the US is often reported to be about 2 cases per million population (Constantinescu et al 2004, Loirat and Frémeaux-Bacchi 2011).The estimate for Europe is similar at 1.5-1.8 cases per million population (Salvadori and Bertoni 2013). The European HUS registry identified 167 cases of aHUS diagnosed between 1974 and 2005 and estimated a prevalence of aHUS (defined as D-HUS and HUS not associated with *E coli*), or recurrent HUS to be 3.3 cases per one million population aged 18 years or less (Zimmerhackl et al 2006). A chart review study from Norway suggested an incidence of any HUS to be 0.5 per 100,000 children, of which 19% was found to be aHUS (defined as D-HUS) (Jenssen et al 2014). The Northern Italian HUS network identified 12 cases of paediatric aHUS between 2003 and 2012, resulting in an incidence estimate of 0.75 cases per one million children (under age 18) and a point prevalence estimate of 10.7 cases per million children. However, given the 8.4% early case fatality rate, the true point prevalence was estimated to be 9.4 per million (Ardissino et al 2016).

Demographics of the population in the authorised indication –age, gender, racial and/or ethnic origin and risk factors for the disease:

In the available literature, the aHUS population is largely Caucasian; however, it should be noted that these studies are primarily in Western Europe and North America (Constantinescu et al 2004, Dragon-Durey et al 2010, Fakhouri et al 2016, M11-001 2015, Maga et al 2010, Sellier-Leclerc et al 2007, Westra et al 2010).

Age of onset for HUS can fall within a huge range, but the earliest cases (onset during the 6 months of life), are suggestive of aHUS (Loirat and Frémeaux-Bacchi 2011). Data suggest that the average age of onset may be significantly lower in aHUS cases compared to HUS patients with diarrhoea (Constantinescu et al 2004, Zimmerhackl et al 2006).

In a European paediatric aHUS registry, 56% of patients were male and the mean age of onset among the 167 cases was 25 months, with many cases developing within the first year of life (Zimmerhackl et al 2006). In a French cohort of 46 paediatric aHUS patients, 56% were male and 70% experienced onset before the age of 2 years (Sellier-Leclerc et al 2007). Similarly, among 27 Canadian children with aHUS (defined as D-HUS), 63% were male and

the median age of onset was 2 years (Constantinescu et al 2004). In the Northern Italian HUS Network, the median age of onset among paediatric aHUS cases was 3 years and 55% were male (Ardissino et al 2016). In 45 aHUS patients who were also positive for anti-factor H autoantibodies, the median age of onset was 8.5 years among 38 children (66% male) between the ages of 8 months and 14 years; the median age of onset in 7 adults (100% male) between the ages of 28 and 52 was 41 years (Dragon-Durey et al 2010). In a larger study that includes adult and paediatric patients, the gender distribution was nearly 1:1 (Noris et al 2010), and in a registry that included adult and paediatric aHUS patients in German-speaking Europe, 40% of identified cases were male and the mean age at diagnosis was 30 years, but this registry only included adults initially before being expanded to children and adolescents (Sullivan et al 2010).

In an adult aHUS cohort taking part in a phase 2 trial for eculizumab, the mean age at diagnosis was 40 years, with 66% of cases in the 45 to 65-year-age range; 68% of patients were female (Fakhouri et al 2016). The median age at onset among paediatric patients in the Alexion registry was 3.4, and the median age of onset of aHUS symptoms among adults in this registry was 36.2. In the paediatric patients enrolled in this registry, there was a higher proportion of male participants (58%), compared to a higher proportion of females among the enrolled adults (62.8%) (Registry Study M11-001). A review article of aHUS cites a number of predisposing conditions for aHUS, including: complement regulatory defects (estimated to account for about half of the cases of aHUS), *S pneumoniae,* human immunodeficiency virus, some drugs (eg, chemotherapy, quinine, immunosuppressive agents, oral contraceptives and some illicit drugs), pregnancy, systemic disease (eg, systemic lupus, scleroderma and anti-phospholipid-syndrome), malignancy, and combined methylmalonic aciduria and homocystinuria (Kavanagh et al 2006).

Risk factors

The most common aHUS-related genetic abnormality is in complement factor H (CFH), affecting approximately 11% to 29% of aHUS cases based on aHUS registry data, followed by member co-factor protein, complement factor I (CFI), and C3, each affecting approximately 2% to 17% of patients, and finally Factor B and thrombomodulin, each affecting approximately 0-5% of patients (Maga et al 2010, Salvadori and Bertoni 2013). A similar ranking of the frequency of aHUS-related genetic mutations was found among adult aHUS patients in a phase 2 trial to assess the efficacy of eculizumab. Overall, 49% of cases had a genetic abnormality: 24% had a CFH mutation, 10% had a C3 mutation, 5% had a CFI, and 5% had a membrane cofactor protein (MCP) mutation (Fakhouri et al 2016). Mutations in the diacylglycerol kinase epsilon gene have also been shown to be associated with development of aHUS and patients with this recessive mutation typically present before 1 year of age, have persistent hypertension, haematuria and proteinuria, and later develop chronic kidney disease (Lemaire et al 2013).

The role of genetic mutations in risk for aHUS may be greater at younger ages: in a cohort of 46 paediatric aHUS cases in France, genetic mutation was associated with younger age of onset (Sellier-Leclerc et al 2007), and in a German aHUS registry, 20% of cases in patients aged 20 years or less were associated with a known mutation, but only 9% of those over the age 20 were (Sullivan et al 2010).

A German aHUS registry estimated that 28% of aHUS cases experienced a recurrence (Sullivan et al 2010). CFH and MCP haplotypes have been shown to increase the likelihood of aHUS recurrence (Noris et al 2010). A genetic study of 45 paediatric aHUS cases in Belgium and the Netherlands, found that those with mutations in complement regulating genes were more likely to experience aHUS relapse (65% relapsed) versus those without a mutation (32% relapsed) (Geerdink et al 2012). A prospective follow-up of 45 aHUS patients who tested positive for anti-factor H autoantibodies observed a 58% recurrence rate, with 68% of relapses occurring within 6 months of initial onset (Dragon-Durey et al 2010).

Fewer than 20% of aHUS cases are believed to be familial (Noris and Remuzzi 2009, Sullivan et al 2010). Of the 732 aHUS patients enrolled in the Alexion-sponsored aHUS registry, approximately 16% had a family history of aHUS (Registry Study M11-001). A review of aHUS-related genetic abnormalities and clinical outcomes concluded that patients with familial aHUS have poorer prognoses, and that it is associated with an increased risk for relapse (Geerdink et al 2012, Noris and Remuzzi 2009).

Frequently, aHUS is triggered by an infectious event, usually an upper respiratory infection or gastroenteritis. This occurs in approximately 50% of adult cases and 80% of paediatric cases (Loirat and Frémeaux-Bacchi 2011, Salvadori and Bertoni 2013). It was also found that an infectious trigger was more common in those with known MCP mutations versus those with no mutations or with CFH mutation only (Caprioli et al 2006). Pregnancy is a notable trigger for aHUS. Out of 100 female aHUS cases in a retrospective study conducted between 2000 and 2008, 21 were triggered by pregnancy; of these, 18 (86%) had a complement abnormality (Fakhouri et al 2010). The risk of pregnancy-triggered aHUS was highest during second pregnancies and the mean age of onset was younger in pregnancy-related aHUS patients (26 years) than among the women whose aHUS was not pregnancy related (33 years). It is estimated that, among pregnancy-related aHUS, 20% of cases develop during pregnancy and 80% develop during the postpartum period (Salvadori and Bertoni 2013).

The main existing treatment options:

Prior to the introduction of eculizumab and ravulizumab, only supportive treatment for patients with aHUS were available, such as transfusions of red blood cells and platelets, dialysis (if the disease progressed to a kidney failure which may even require a kidney transplant), plasma infusion or plasma exchange (Loirat and Frémeaux-Bacchi 2011). The role of plasma in this condition is not completely elucidated.

Antibiotics may be used when aHUS is precipitated by an infectious event. Because severe hypertension is common in aHUS, drugs to control blood pressure may be used (Kavanagh et al 2006).

Natural history of the indicated condition in the (untreated) population, including mortality and morbidity:

Up to 25% of aHUS patients may die in the acute phase of the disease and approximately 50% may require ongoing renal replacement therapy (Kavanagh et al 2006, Rafiq et al 2015). However, although the course of aHUS is typically more severe than that of D+ HUS and can indeed be life-threatening, there is a wide range of clinical outcomes within aHUS and some patients have only mild disease while others progress to severe outcomes or death (Kavanagh et al 2006).

The onset of aHUS is typically sudden, and children may typically present with symptoms including pallor, general distress, vomiting, loss of appetite, and fatigue while adults more typically present with fatigue and general distress. Upon clinical investigation, most patients demonstrate the three hallmark symptoms defining HUS, including haemolytic anaemia, thrombocytopenia and renal impairment. However, when diagnosis is delayed, patients may progress to more severe symptoms, including hyperkalaemia, acidosis, and volume overload with arterial hypertension and hyponatraemia. More than a half of patients typically receive dialysis at diagnosis and approximately 20% of patients have extra-renal complications with neurologic complications being the most frequent (Loirat and Frémeaux-Bacchi 2011).

In a retrospective paediatric cohort study conducted in Northern Italy between 2003 and 2012, one out of 12 cases of aHUS died, due to sepsis, for a case fatality rate of approximately 8% (Ardissino et al 2016). Another Italian study identified 9 cases of aHUS (defined as D-HUS): five of those cases had a recurrence, one of whom died during a combined kidney-liver transplant surgery (Micheletti et al 2010). Four patients (9%) in a Dutch and Belgian paediatric cohort of 45 aHUS patients died, one during the acute phase of the disease and three others later (Geerdink et al 2012). The long-term (average of 39 months) follow-up of 45 international aHUS patients who were positive for anti-factor H autoantibodies, revealed that 4 (9%) patients had died. Two deaths were in children and the causes were pulmonary hypertension and unexplained (following a dialysis session). The other two deaths were among adults, one from cardiac insufficiency and the other from an unknown cause (Dragon-Durey et al 2010). Finally, in a French cohort of 46 aHUS patients, 4 died within a few weeks or months of symptom onset, and within a year 37% had either died or developed end-stage renal disease (ESRD) (Sellier-Leclerc et al 2007).

The risk of death from aHUS is greatly increased among those with CFH mutations. A case-control study that included patients from the International Registry of Recurrent and Familial HUS found a statistically significant associated between CFH mutation and death. In

this study, 5% of patients with no mutations died following their first episode and 30% of patients with a CFH mutations died following their first episode. This same pattern continued upon long-term follow-up (Caprioli et al 2006). A more recent analysis of the same registry showed that, in addition to CFH mutation, a thrombomodulin irregularity is also associated with an increased risk of death. Upon their first aHUS episode, 19% and 31% of patients with CFH and thrombomodulin mutations died and this pattern held for at least three years. The authors noted that patients with familial aHUS tend to have a poor prognosis, with 50-80% progressing to ESRD or death (Noris et al 2010, Noris and Remuzzi 2009). One study noted that increased creatinine level at first aHUS episode is significantly correlated with the risk for ESRD or death during the first year (Sellier-Leclerc et al 2007).

Important co-morbidities:

- Renal disease
- Arterial hypertension
- Central nervous system disease
- Cardiovascular disease

2.1.3 Refractory generalised myasthenia gravis

Incidence and prevalence:

A systematic review focused on 31 primarily European studies published between 1980 and 2007, estimated that the annual incidence of myasthenia gravis (MG) is approximately 30 per million persons. The authors found increased incidence over time and suggested that prospective studies, which found incidences ranging from 20 to 30 per million per year, may be most accurate (McGrogan et al 2010).

Similarly, a recent study conducted among the national registers in Sweden reported an annual incidence of 29 per million in 2016 (Westerberg and Punga 2020).

The incidence of MG has been shown to increase with age, with the annual incidence in paediatric patients estimated to be between 1.0 and 5.0 per million persons (McGrogan et al 2010, Popperud et al 2017). Increasing incidence with age has been observed among the paediatric population as well with an annual incidence of 0.9 per million and 3.1 per million among those aged 1 to 11 years and 12 to 17 years, respectively (Popperud et al 2017).

While a wide range of prevalence estimates have been reported in several epidemiological studies, a recent and robust study based in Sweden identified cases with a primary or secondary diagnosis of MG or two or more prescriptions of pyridostigmine or ambenonium and reported a prevalence of 361 cases per million in 2016 (Westerberg and Punga 2020).

The prevalence of MG in paediatric patients in Norway has been estimated as 3.6 and 13.8 cases per million in 2013 and 2003, respectively (Popperud et al 2017).

About 75% of diagnosed prevalent cases of MG reported in European studies are of the generalised type (Fang et al 2015, Joensen 2014, Lefter et al 2017, Pallaver et al 2011, Santos et al 2016). The most frequently found auto-antibodies among patients with generalised MG (gMG) are directed against acetylcholine receptor (AChR) and muscle-specific kinase (MuSK). About 70% to 88% of patients with gMG are AChR antibody-positive, and 7% to 12% are MuSK antibody-positive (Anil et al 2020, Hendricks et al 2019, Oh 2009, Tomschik et al 2020).

Among children diagnosed with juvenile myasthenia gravis, about 66% are diagnosed with gMG and about 70% of the gMG patients are positive for AChR antibodies (Mansukhani et al 2019, VanderPluym et al 2013).

Although data on the prevalence of refractory MG are scarce, it is estimated that 7% to 15% of prevalent MG cases are refractory (Boscoe et al 2019, Engel-Nitz et al 2018, Suh et al 2013).

Demographics of the population in the authorised indication –age, gender, racial and/or ethnic origin and risk factors for the disease:

As the incidence of MG typically increases with age and mortality due to MG itself is low, the highest disease prevalence is observed in older age groups (Carr et al 2010). Most studies show the incidence of MG increasing for men in the 60 to 80-year-old age group. However, the incidence of MG generally has a bimodal age distribution in women with a peak in the 20 to 40-year-old age group and then again in the 50 to 70-year-old age group (Carr et al 2010, McGrogan et al 2010).

Although demographic data specific to refractory gMG are limited, a recent retrospective chart review conducted at a tertiary neuromuscular clinic found that 19 of 128 MG patients were found to have refractory gMG. In this population, patients with refractory gMG were more likely than other MG patients to be female (74% compared to 47%) and younger at disease onset (36 years versus 60 years) (Suh et al 2013).

Risk factors

Most studies suggest that gMG incidence and prevalence increase with age, although there is some variation by study (Gattellari et al 2012, McGrogan et al 2010). In a population-based study using the Taiwan National Health Insurance Research Database, a family history of systemic lupus erythematosus was found to be associated with an increased risk of gMG with a relative risk of 2.95 after adjustment for age, sex, place of residence, income, occupation, and family size (Kuo et al 2015).

Another study in this database found that risk of gMG was elevated in patients with allergic conjunctivitis, allergic rhinitis, Hashimoto's thyroiditis, Graves' disease and diabetes mellitus (Yeh et al 2015).

In a meta-analysis, some polymorphisms in the human leukocyte antigen (*HLA*)-DRB1 gene were found to be associated with increased risk of late-onset MG (Ling et al 2020).

Thymomas are also a risk factor with about 30% of patients with thymoma developing MG (Marx et al 2013).

The main existing treatment options:

Prior to the introduction of eculizumab and ravulizumab, there were no other targeted therapies available to help modify the disease course; therefore, refractory gMG patients would continue experiencing episodes of inflammation despite established immunosuppressive treatment.

The current first-line therapy for the treatment of MG is pyridostigmine; other acetylcholinesterase inhibitors, including neostigmine and ambenonium chloride, can also be used to treat symptomatic MG. Patients who do not fully respond to treatment for MG symptoms with acetylcholinesterase inhibitors are typically given immunosuppressive drugs (eg, including corticosteroids, azathioprine (AZA), mycophenolate mofetil (MMF), tacrolimus, ciclosporin). Drugs that can negatively impact neuromuscular transmission, such as some types of antibiotics, are typically avoided in patients with MG (Gilhus and Verschuuren 2015). Plasma exchange and intravenous immunoglobulin are sometimes used to treat acute exacerbations of MG (Meriggioli and Sanders 2009). Majority of current available therapies are focusing on autoantibody reduction.

Natural history of the indicated condition in the (untreated) population, including mortality and morbidity:

Muscle weakness is a primary sign and symptom of MG MG (Gilhus and Verschuuren 2015, Meriggioli and Sanders 2009). Patients with MG most commonly present with ocular symptoms and typically progress to generalised weakness within 2 years of disease onset. Facial and bulbar weakness are also common in MG. Weakness can extend to limb-girdle and respiratory muscles. The involvement of respiratory muscles can be life-threatening and require immediate intervention. The course of gMG varies by patient, and most patients experience at least one exacerbation of their symptoms, which can be triggered by certain stressors (eg, some medications, infection, surgery, emotional stress) (Hehir and Silvestri 2018, Meriggioli and Sanders 2009). Additionally, 15% to 20% of patients with gMG experience a myasthenic crisis, usually within 3 years of diagnosis (Hehir and Silvestri 2018). Remission may occur in 10% to 20% of patients (Grob et al 2008).

Hospitalisations for MG exacerbations are common, with the need for respiratory support, including mechanical ventilation secondary to respiratory failure (eg, during myasthenic crisis), with no substantial improvement in length of hospitalisation or in-hospital mortality from 1991-1992 to 2001-2002 (Souayah et al 2009). Patients with refractory MG experience significantly more hospital admissions, emergency room visits, myasthenic crises and exacerbations compared to patients with non-refractory MG (Boscoe et al 2019, Engel-Nitz et al 2018).

Patients with MG that have persistent symptomatology are likely to have diminished work capacity, difficulty caring for themselves and for others, and require assistance in their activities of daily living including grooming or household chores (Boscoe et al 2019, Harris et al 2019).

Mortality in MG has decreased steadily from 1940 through 2000 due to improved treatment and respiratory intensive care (Grob et al 2008). Most recently, a mortality rate of 1.51 per 100 patients has been reported among Swedish MG patients enrolled in the Swedish National Patient Register from 2006 to 2016, which is comparable to the Swedish general population (Westerberg and Punga 2020). Similarly, a retrospective study conducted in Austria using medical records of patients with gMG from 2000 to 2018 reported that the observed mortality rate among the gMG patients in the study was consistent with the general population (Tomschik et al 2020). Additionally, it has been reported that the mortality rate during one year of follow-up was twice as high for patients with refractory MG compared those with non-refractory MG (Engel-Nitz et al 2018).

Important co-morbidities:

- Diabetes mellitus
- Other autoimmune disease (eg, autoimmune thyroid disease, systemic lupus erythematosus, rheumatoid arthritis)
- Respiratory insufficiency
- Malignancy
- Infection
- Dyslipidaemia
- Depression

2.1.4 Neuromyelitis optica spectrum disorder

Incidence and prevalence:

Neuromyelitis optica spectrum disorder (NMOSD) is extremely rare. The published estimates of incidence and prevalence vary widely, most notably due to difference in methodology concerning case ascertainment. Most studies rely on diagnosed cases, and do not account for potential misdiagnoses, especially common in older studies.

In a study evaluating total prevalence of neuromyelitis optica (NMO)/NMOSD in the US (Olmstead County) and French West Indes (Martinique), the age- and sex-adjusted incidence was approximately 10 times higher in Martinique than in Olmstead County: 0.73 per 100,000 compared to 0.07 per 100,000, and prevalence was 10.0 and 3.9 per 100,000, respectively. AQP-4 seropositivity was 83% in Olmstead County and 79% in Martinique. In both areas, blacks had a higher incidence and prevalence than whites (Flanagan et al 2016). A population-based study in Denmark, from 1998-2008 using the Danish National Patient Registry (>99% Caucasian) and a similar disease definition estimated the total annual incidence (rather than diagnosed cases only) to be 0.4 per 100,000 and prevalence to be 4.4 per 100,000, with 62% of patients having antibodies to aquaporin-4 (AQP-4) (Asgari et al 2011).

Of interest, although the prevalence in the Danish study was quite similar to that in Caucasians in the US study (4.4 compared to 3.9 per 100,000) (Flanagan et al 2016), the incidence in the Danish study was much higher than that in the US. A regional study in south east Wales, which identified cases from a regional neuroinflammatory registry, estimated the (diagnosed) prevalence of NMOSD in 2010 to be 1.96 per 100,000 and 10 of the identified 14 cases (71%) had antibodies to AQP-4 (Cossburn et al 2012).

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

NMOSD is more common in women than in men, with an average age at onset typically between 30-40 years, and NMOSD varies by race, being more common in blacks (Flanagan et al 2016). A multicentre retrospective study in the US published in 2012 identified 182 NMOSD, with a mean age at onset of 41.1 years, a female to male ratio of 6.5:1, and most common racial groups of white (47.6%) or of African descent (36.9%). The authors noted that while blacks represent approximately 12% of the US population, they made up nearly 37% of the NMOSD patients in the study (Mealy et al 2012).

In a study of 186 patients with NMOSD conducted between January 2012 and March 2013 using the German Neuromyelitis Optica Study Group registry, the female to male ratio was 23:1 for females ages of 15 to 40 among those who were AQP-4 antibody (AQP4Ab) seropositive. Women were more likely to be AQP4Ab seropositive than men (92% versus

55%, p<0.001) (Borisow et al 2017). Similarly, in a multicentre study of 175 Caucasian patients in Germany with NMOSD identified between August 2009 and August 2011, the female to male ratio was higher among those who were seropositive when compared to those who were seronegative with 83.3% of females being seropositive and only 48% of males being seropositive (Jarius et al 2012).

A recent study from the United Kingdom (UK), which evaluated patients who were seen at the National NMO clinic over a 4-year period, found that 73% of patients who satisfied the 2015 Wingerchuk criteria for NMOSD were positive for the AQP4Ab (Hamid et al 2017).

Risk factors

As shown above, race and female gender represent potential risk factors for NMOSD. Although infections are believed to play a role in some autoimmune diseases, the specific role in NMOSD is unclear.

Risk factors for relapse of NMOSD are varied. In a multicentre study of 175 Caucasian patients in Germany with NMOSD identified between August 2009 and August 2011, relapse was more common in patients who were AQP4Ab seropositive than in patients who were seronegative (92.7% v. 72.6%, p<0.008) (Jarius et al 2012).

The main existing treatment options:

Prior to approval of eculizumab as a treatment for NMOSD, only supportive treatment was available such as corticosteroids and other immunosuppressive therapies, including AZA, rituximab, MMF, methotrexate, and mitoxantrone. The use of these supportive medications was based on clinical experience and consensus (Trebst et al 2014). However, despite these supportive therapies, a significant number of patients (> 50%) continued to have relapses, resulting in additional and permanent neurologic deficits and disability.

The primary treatment for an NMOSD attack is high-dose intravenous methylprednisolone, which is followed in some cases by a steroid tapering for 2 weeks to 2 months after initial treatment. Plasma exchange is also recommended if steroids are not successful in controlling the symptoms and for complex cases, cyclophosphamide has been added to the regimen. For prevention of relapses, immunosuppressive treatments include AZA, rituximab, MMF, methotrexate, oral corticosteroids, and mitoxantrone (Kimbrough et al 2012, Sherman and Han 2015).

Natural history of the indicated condition in the (untreated) population, including mortality and morbidity:

Relapse is common in NMOSD. In a retrospective multicentre study of 175 Caucasian patients in Germany with NMOSD identified between August 2009 and August 2011, patients relapsed 5 times on average over an average disease course of 57.5 months, with 89.1% of the study population experiencing at least one relapse (Jarius et al 2012).

Mortality in NMOSD is a significant risk following diagnosis and morbidity is significant and may include visual disabilities and/or motor disabilities during attacks, and some patients may experience extended or permanent disability (Kitley et al 2014). In a study of the clinical outcomes of 106 consecutively enrolled AQP4Ab positive NMOSD patients in the UK and Japan between 2006 and 2010, 10 patients (9.4%) died after a median disease duration of 99 months, and 7 of the 10 deaths were cited as being directly attributable to NMOSD or complications of NMOSD. The mean age at death in this population was 52 years and older age was strongly predictive of death, but gender, onset attack severity and type of onset attack were not associated with death. Further, morbidity was significant with 18% experiencing permanent visual disability, 34% experiencing permanent motor disability, and 23% experiencing wheelchair dependency during the follow-up period. Of the 86 patients who experienced a relapse, 62% had attacks of optic neuritis as well as longitudinally extensive transverse myelitis (LETM), 18% had only LETM, and 9% had relapsing optic neuritis (Kitley et al 2014).

Based on data from a multicentre study of 9 sites across the world of 258 patients with NMOSD, brainstem symptoms were reported in 81 patients (31.4%) and occurred more commonly in non-Caucasian population ($p<0.05$). Most frequently reported brainstem symptoms included uncontrolled vomiting and intractable hiccups (Kremer et al 2014).

Important co-morbidities:

- Infection
- Severe pain
- Neurological complications (bowel/bladder, myopathy, blindness)

2.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage

Eculizumab is species specific, and during the early non-clinical development phase, it was shown that it does not cross-react with the C5 complement component from a range of commonly used non-human primate and non-primate species.

As they would not have been predictive of effects in humans, the following studies have not been conducted:

- Non-clinical safety pharmacology studies
- Genotoxicity studies (according to Committee for Medicinal Products for Human Use [CHMP]/International Council for Harmonisation [ICH]/302/95 Guideline)
- Carcinogenicity studies (according to CHMP/ICH/302/95 Guideline).

To provide information on the potential tissue toxicity of long-term inhibition of C5 and to evaluate the influence of such inhibition on reproductive function, studies have been performed in mice, using the surrogate murine anti-mouse C5 antibody (BB5.1mAb).

Additional non-clinical studies are not planned, and appropriate instruction is provided in the product information to special populations on the use of eculizumab.

2.2.1 Toxicity

Key issues identified from acute or repeat-dose toxicity studies

26-week repeat dose toxicity study in CD-1 mice

This study in CD-1 mice provided evidence that extensive inhibition of C5 under normal circumstances is not associated with any significant toxicity or risk even when this inhibition is continuous and in a long term.

Moreover, it showed no cytotoxic or proliferative activities suggestive of carcinogenic risk at dose levels up to 60 mg/kg/week.

Reproductive/developmental toxicity

Three malformations were noted in high-dose animals of the embryo-foetal study – two cases of unilateral retinal dysplasia and one umbilical hernia. Animal reproduction studies have not been conducted with eculizumab, due to lack of pharmacologic activity in non-human species.

There are no well-controlled studies in pregnant women treated with eculizumab. Data on a limited number of pregnancies exposed to eculizumab 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 treatment be considered necessary during pregnancy, a close maternal and foetal monitoring according to local guidelines is recommended.

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.

Segment I, II and III reproduction studies in CD-1 mice

These studies were conducted to assess any potential effect of C5 inhibition on reproductive processes, ie, fertility and early embryonic development, embryo-foetal development, and pre- and postnatal toxicity in CD-1 mice.

The only observations of potential concern from the three reproduction studies with BB5.1mAb are the three malformations – two cases of unilateral retinal dysplasia and one umbilical hernia – in high dose animals of the embryo-foetal study. As the cases of dysplasia were unilateral with no other eye abnormalities such as microphthalmia, anophthalmia, haemorrhage, etc., the two cases of retinal dysplasia were considered to be a processing artefact. Regarding the umbilical hernia, it is not possible to assign the finding either as treatment related or non-treatment related.

2.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

This section summarises exposure data from the clinical development programmes for eculizumab at the time of submission (by indication). The overall cumulative exposure to eculizumab is provided in Table 2-1.

Considering the unique nature of diseases treated by eculizumab, characteristics of the target populations and corresponding variable design of clinical trials, the exposure data by duration of exposure or demographic characteristics are not pooled across the entire development programme, but only across the individual development programmes for each indication (ie, PNH, aHUS, refractory gMG, and NMOSD).

Table 2-1 Overall exposure to eculizumab within the clinical development programme at the time of submissions (all indications)

Indication	Patients	Person time (patient-years)
PNH	**231**	**551.6**
Adult patients	224	550.0
Paediatric patients	7	1.6
aHUS	**130**	**178.3**
Adult patients	83	129.2
Paediatric patients	47	49.1
Refractory gMG[a]	**134**	**153.7**
Adult patients	123	135.8
Paediatric patients	11	17.9
NMOSD[b]	**96**	**170.0**
Adult patients	96	170.0
Paediatric patients	0	0

[a] Data in adult population are based on ECU-MG-301 final analysis and ECU-MG-302 interim database lock (cut-off date on 21 September 2016). Data from Study C08-001 are not available. Data in paediatric population are based on ECU-MG-303 26-week Primary Evaluation Treatment Period and Extension Period up to the data cut-off date 06 January 2022.

[b] Data based on ECU-NMO-301 final analysis.

aHUS, atypical haemolytic uraemic syndrome; gMG, generalised myasthenia gravis; NMOSD, neuromyelitis spectrum disorder; PNH, paroxysmal nocturnal haemoglobinuria.

2.3.1 PNH clinical development programme

Table 2-2 Clinical trial exposure to eculizumab by study in PNH patients (adult and paediatric population)

PNH studies	Patients	Mean duration	Person time (patient-years)
C04-001, C04-002 and X03-001A extended by E05-001	195	28.7 months	543.3
C07-001	29	2.8 months	6.7
M07-005	7	12 weeks	1.6
Total	**231**	-	**551.6**

PNH, paroxysmal nocturnal haemoglobinuria.

Table 2-3 Demographic characteristics (age group, sex and race) for PNH studies (adult and paediatric population)

PNH studies	C04-001, C04-002 and X03-001A extended by E05-001 (N=195)	C07-001 (N=29)	M07-005 (N=7)	Total (N=231)
Sex, n (%)				
Male	89 (46)	14 (48)	4 (57)	107 (46)
Female	106 (54)	15 (52)	3 (43)	124 (54)
Age (years), N (%)				
<18	0	0	7 (100)	7 (3)
≥18 to <65	179 (92)	28 (97)	0	207 (90)
≥65	16 (8)	1 (3)	0	17 (7)
Race, n (%)				
Asian	6 (3)	29 (100)	0	35 (15)
Black	7 (4)	0	2 (29)	9 (4)
Caucasian	176 (90)	0	5 (71)	181 (78)
Other	6 (3)	0	0	6 (3)

PNH, paroxysmal nocturnal haemoglobinuria.

2.3.2 aHUS clinical development programme

Table 2-4 Clinical trial exposure to eculizumab by study in aHUS patients (adult and paediatric population)

Duration (months)	aHUS prospective trials (N=100)	All aHUS trials (N=130)
Mean (SD)	19.13 (11.788)	16.46 (11.720)
Median	16.821	14.554
Min - Max	0.46 - 43.14	0.46 - 43.14
Total person time (patient-years)	**159.40**	**178.27**

Prospective studies: C08-002A/B; C08-003A/B; C10-003; C10-004. Retrospective study C09-001r
aHUS, atypical haemolytic uraemic syndrome; max, maximum; min, minimum; SD, standard deviation.

Table 2-5 Clinical trial exposure by duration in aHUS studies (adult and paediatric population)

Duration of exposure	aHUS prospective trial		All aHUS trials	
	Patients (N)	Person time (patient-years)	Patients (N)	Person time (patient-years)
At least 2 weeks	100	159.40	130	178.27
At least 4 weeks	98	159.33	126	178.09
At least 12 weeks	97	159.23	121	177.43
At least 26 weeks	92	157.28	109	172.92
At least 52 weeks	67	140.88	73	149.13
At least 64 weeks	58	130.93	63	138.07
At least 78 weeks	48	117.64	49	119.49
At least 2 years	29	83.90	29	83.90
Total	**100**	**159.40**	**130**	**178.27**

Prospective studies: C08-002A/B; C08-003A/B; C10-003; C10-004. Retrospective study C09-001r
aHUS, atypical haemolytic uraemic syndrome.

Table 2-6 Clinical trial exposure in aHUS studies by age and sex (adult and paediatric population)

Age group (years)	aHUS prospective trials				All aHUS trials			
	Patients (N)		Person time (patient-years)		Patients (N)		Person time (patient-years)	
	Male	Female	Male	Female	Male	Female	Male	Female
<23 months	2	3	2.95	4.14	4	6	4.67	5.27
≥23 months to <5	2	3	1.31	1.65	4	4	3.01	2.05
≥5 to <12	5	3	5.52	3.48	8	7	8.1	5.82
≥12 to <18	4	6	4.42	13.69	6	8	4.87	15.27
≥18 to <45	19	31	32.13	51.61	22	37	33.48	56.83
≥45 to <65	6	12	11.78	21.66	8	12	12.14	21.66
≥65 to <75	0	3	0	4.76	0	3	0	4.76
≥75	0	1	0	0.32	0	1	0	0.32
Total	**38**	**62**	**58.11**	**101.3**	**52**	**78**	**66.29**	**111.98**

Prospective studies: C08-002A/B; C08-003A/B; C10-003; C10-004. Retrospective study C09-001r
aHUS, atypical haemolytic uraemic syndrome.

Table 2-7 Clinical trial exposure in aHUS studies by race (adult and paediatric population)

Race	aHUS prospective trials		All aHUS trials	
	Patients (N)	Person time (patient-years)	Patients (N)	Person time (patient-years)
White	88	141.34	111	154.65
Black or African American	5	9.72	7	10.73
Asian	4	2.60	5	3.98
Other	3	5.74	7	8.91
Total	**100**	**159.40**	**130**	**178.27**

Prospective studies: C08-002A/B; C08-003A/B; C10-003; C10-004. Retrospective study C09-001r
aHUS, atypical haemolytic uraemic syndrome.

2.3.3 Refractory gMG clinical development programme

Table 2-8 Clinical trial exposure to eculizumab by study in refractory gMG (paediatric population)

Refractory gMG study	Patients (N)	Mean duration (days)	Person time (patient-years)
Paediatric population [a]			
ECU-MG-303	11	594.8	17.9

[a] Data in paediatric population are based on ECU-MG-303 26-week Primary Evaluation Treatment Period and Extension Period up to the data cutoff date 06 January 2022.

gMG, generalised myasthenia gravis.

Table 2-9 Clinical trial exposure by duration in refractory gMG studies (adult and paediatric population)

Duration (weeks)	Patients (N)	Person time (patient-years)
Adult population [a]		
<13	4	0.6
≥13 to <26	6	2.2
≥26 to <39	27	16.0
≥39 to <52	14	12.0
≥52	72	105.0
Total	**123**	**135.8**
Paediatric population [b]		
<13	0	0
≥13 to <26	1	0.5
≥26 to <39	1	0.6
≥39 to <52	2	1.6
≥52	7	15.2
Total	**11**	**17.9**

[a] Data in adult population are based on ECU-MG-301 final analysis and ECU-MG-302 interim database lock (cut-off date on 21 September 2016). Data from Study C08-001 are not available.

[b] Data in paediatric population are based on ECU-MG-303 26-week Primary Evaluation Treatment Period and Extension Period up to the data cut-off date 06 January 2022.

gMG, generalised myasthenia gravis.

Table 2-10 Clinical trial exposure to eculizumab by age group and sex in refractory gMG studies (adult and paediatric population)

Age group (years)	Patients (N)			Person time (patient-years)		
	Male	Female	Total	Male	Female	Total
<12	0	0	0	0	0	0
≥12 to <18	2	9	11	4.6	13.3	17.9
≥18 to <65	25	76	101	25.4	83.2	108.6
≥65	16	6	22	19.6	7.6	27.2
Total	**43**	**91**	**134**	**49.6**	**104.1**	**153.7**

gMG, generalised myasthenia gravis.

Table 2-11 Clinical trial exposure to eculizumab by race in refractory gMG studies (adult and paediatric population)

Race	Patients (N)	Person time (patient-years)
Adult population [a]		
Asian	19	18.0
Black or African American	2	2.1
White	94	106.7
Multiple	1	1.2
Unknown	1	1.5
Other	6	6.4
Total	**123**	**135.8**
Paediatric population [b]		
Asian	3	5.6
Black or African American	5	8.8
White	2	1.3
Other	1	2.2
Total	**11**	**17.9**

[a] Data in adult population are based on ECU-MG-301 final analysis and ECU-MG-302 interim database lock (cutoff date on 21 September 2016). Data from Study C08-001 are not available.

[b] Data in paediatric population are based on ECU-MG-303 26-week Primary Evaluation Treatment Period and Extension Period up to the data cutoff date 06 January 2022.

gMG, generalised myasthenia gravis.

2.3.4 NMOSD clinical development programme

Table 2-12: Clinical trial exposure to eculizumab by study in NMOSD patients (adult population)

NMOSD studies	Patients (N)	Mean treatment duration (SD)	Person time (patient-years)
ECU-NMO-301	96	92.41 weeks (56.570)	170.0

Data based on ECU-NMO-301 final analysis.
NMOSD, neuromyelitis optica spectrum disorder; SD, standard deviation.

Table 2-13: Clinical trial exposure to eculizumab by duration in NMOSD studies (adult population)

Duration of exposure (weeks)	Patients (N)	Person time (patient-years)
<13	5	0.6
≥13 to <26	8	2.6
≥26 to <39	8	5.3
≥39 to <52	8	6.7
≥52	67	154.8
Total	96	170.0

Data based on ECU-NMO-301 final analysis.
NMOSD, neuromyelitis optica spectrum disorder.

Table 2-14 Clinical trial exposure to eculizumab by age group and sex in NMOSD studies (adult population)

Age group (years)[a]	Patients (N)		Person time (patient-years)	
	Male	Female	Male	Female
<18	0	0	0	0
≥18 to <65	8	82	13.2	140.0
≥65	0	6	0.0	16.8
Total	**8**	**88**	**13.2**	**156.8**

Data based on ECU-NMO-301 final analysis.
[a] Age group is determined from the age at first dose of study drug in Study ECU-NMO-301.
NMOSD, neuromyelitis optica spectrum disorder.

Table 2-15 Clinical trial exposure to eculizumab by race and ethnic origin in NMOSD studies (adult population)

Race	Patients (N)	Person time (patient-years)
Asian	37	67.4
American Indian or Alaska Native	1	1.5
Black or African American	9	9.3
White	46	88.6
Other	1	1.5
Unknown	2	1.7
Total	**96**	**170.0**
Ethnic origin	**Patients (N)**	**Person time (patient-years)**
Hispanic or Latino	13	17.8
Not Hispanic or Latino	78	144.1
Not reported	4	7.5
Unknown	1	0.6
Total	**96**	**170.0**

Data based on ECU-NMO-301 final analysis.
NMOSD, neuromyelitis optica spectrum disorder.

2.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

2.4.1 Exclusion criteria in pivotal clinical studies within the development programme

Pregnant or breast-feeding women

Reason for exclusion: Women who were pregnant or breastfeeding were excluded from the clinical studies to avoid potential harm to the unborn foetus or breastfed infants.

Is it considered to be included as missing information: No

Rationale: Data in pregnant women treated with SOLIRIS from clinical studies and post-marketing setting, including PNH and aHUS registries, indicate that SOLIRIS is unlikely to increase the risk of malformative or foeto-neonatal toxicity in the PNH and aHUS patient population. There are insufficient data to adequately characterise the safety of SOLIRIS in pregnant women with refractory gMG or NMOSD. The use of SOLIRIS may be considered during pregnancy, if clinically needed.

Limited data available suggest that eculizumab is not excreted in human milk.
Non-clinical reproductive toxicology studies conducted in mice with the murine surrogate molecule BB5.1 identified no adverse effect to pups resulting from consuming milk from treated dams. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SOLIRIS and any potential adverse effects on the breastfed child from SOLIRIS or from the underlying maternal condition.

The missing information "use in pregnant and lactating women" was removed from the list of safety concerns in the EU RMP version 17.2 (variation procedure II/98).

Unresolved *Neisseria meningitidis* infection

Reason for exclusion: Based on eculizumab's mode of action (ie, inhibition of terminal complement), patients are more vulnerable to *Neisseria* spp. infections, especially those caused by *N meningitidis*.

Is it considered to be included as missing information: No

Rationale: This exclusion criterion of clinical development programme remained a contraindication for the administration of SOLIRIS to patients. Moreover, patients treated with SOLIRIS must be vaccinated against all available serotypes of *N meningitidis* or receive prophylactic antibiotics if SOLIRIS is administered before vaccination.

2.4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reaction, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

2.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 2-16 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programmes for PNH, aHUS, refractory gMG, or NMOSD.
Breast-feeding women	Not included in the clinical development programmes for PNH, aHUS, refractory gMG, or NMOSD.
Elderly patients	No age restrictions for use were applied within clinical development programmes for adult patients. Refer to Table 2-3, Table 2-6, Table 2-10, and Table 2-14 for patient exposures sorted by age group.
Patient with relevant comorbidities:	
– Patients with hepatic impairment	Not included in the clinical development programmes for PNH, aHUS, refractory gMG, or NMOSD. SOLIRIS is not generally metabolised in the liver.
– Patients with renal impairment	SOLIRIS is not being excreted through the kidney. Moreover, aHUS clinical development programme included patients with markedly impaired renal function.
– Patients with cardiovascular impairment	Not included in the clinical development programmes for PNH, aHUS, refractory gMG, or NMOSD.
Patients with relevant different ethnic origin	The inclusion and exclusion criteria of the PNH, aHUS, refractory gMG, and NMOSD studies were designed to investigate a broad section of the PNH, aHUS, refractory gMG, and NMOSD population and did not have race as an entry criterion. Refer to Table 2-3, Table 2-7, Table 2-11, and Table 2-15 for patient exposures by race/ethnic origin.

aHUS, atypical haemolytic uraemic syndrome; gMG, generalised myasthenia gravis; NMOSD, neuromyelitis optica spectrum disorder; PNH, paroxysmal nocturnal haemoglobinuria.

2.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

2.5.1 Post-authorisation exposure

2.5.1.1 Method used to calculate exposure

Alexion has been collecting information on the number of patients on commercial treatment since the commercial launch date of SOLIRIS. Exposure was estimated for each quarter starting with the first quarter of 2007 based on aggregate commercial data. Beginning with July 2019 exposure was estimated monthly, again based on aggregate commercial data.

Patients were considered new to treatment, continuing, or discontinued from treatment. The number of new patients and patients who permanently stopped treatment were provided from Alexion's commercial database. The number of continuing patients in a quarter (or month) was determined as the difference between the number of patients on treatment at the end of the previous quarter (or month) and discontinued patients in the current quarter (or month). To simplify the calculation, Alexion assumed that there is no discontinuation among new patients who started treatment in a given quarter (or month).

A quarter is 3 months in duration, and continuing patients were assigned the full 3 months of exposure. As for new and discontinued patients, some patients will have more than 1.5 months of exposure, and some will have less than 1.5 months. As such, new and discontinued patients were assigned 1.5 months of exposure time for a quarter. Monthly estimates similarly assigned 0.5 month of exposure for new and discontinued patients, and a full month for continuing patients.

Person-months were converted to person-years by dividing by 12. The total person-years of exposure for each month or quarter were calculated by adding the person-years of exposure for new, continuing, and discontinued patients for the given month or quarter.

Following an internal review of data handling procedures with respect to patient privacy and confidentiality, collection of commercial data for regions outside of the US were discontinued starting on 01 July 2017. Therefore, in order to estimate patient exposure for regions outside of the US, data that Alexion maintains on vials of product manufactured and distributed were used for exposure estimations. Specifically, the number of new patients and person-years exposure in regions outside of the US were estimated by applying the ratio of product manufactured and distributed by region to the available commercial data and calculated estimates.

The data provided are estimates based on a series of widely used epidemiologic calculation techniques. Regions or groups with smaller cases numbers are particularly prone to perceived "fluctuations" due to the estimation assumptions and data rounding. The most recent data should be regarded as the most accurate representation.

2.5.1.2 Exposure

Table 2-17 provides the estimated number of patients and person time (in patient-years) by region, exposed to eculizumab cumulatively from the International Birth Date (IBD) on 16 March 2007 through 30 June 2024.

Table 2-17 Estimated cumulative post-marketing patient exposure to SOLIRIS by region

Region	Number of patients	Person time (patient-years)
EMEAC	18,315	35,150.38
JAPAC	4,470	10,245.14
LATAM	3,494	7,901.03
CCI [redacted]	17,615	35,741.33
Total	**43,894**	**89,037.88**

EMEAC, Europe, Middle East, Africa, and Canada; JAPAC, Japan, Asia, and Pacific; LATAM, Latin America.

2.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Given to the specific mechanism of action of eculizumab, no illegal use is to be expected.

2.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

2.7.1 Identification of safety concerns in the initial RMP submission

Not applicable.

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

Removal of important risks from the list of safety concerns in the RMP

"Serious haemolysis after drug discontinuation in PNH patients" previously classified as an important potential risk is proposed to be removed from the list of safety concerns, based on the rationale discussed below.

Rationale:

Serious haemolysis following SOLIRIS discontinuation was considered an important potential risk at the time of initial marketing authorisation approval since it was hypothesised that after prolonged period of treatment, the number of PNH red blood cells would increase and upon treatment discontinuation, patients could present with serious haemolysis. However, it is possible that after treatment discontinuation, the long half-life of SOLIRIS results in a gradual complement recovery with slow return of disease rather than a disease rebound.

The post-marketing surveillance via routine and additional pharmacovigilance activities in PNH patients since the IBD did not identify any new and significant information associated with the theoretical possibility of serious haemolysis following discontinuation of eculizumab. No evidence suggesting serious haemolysis after eculizumab discontinuation has been collected. No confirmed case reports of events of serious haemolysis due to discontinuation of eculizumab were received cumulatively since the IBD. All reports of serious haemolysis identified through post marketing were suggestive of inadequate disease control as all respective patients experienced haemolysis while on treatment with SOLIRIS.

"Immunogenicity" previously classified as an important potential risk is proposed to be removed from the list of safety concerns, based on the rationale discussed below.

Rationale:

This potential risk was based on the known potential of all therapeutic proteins to cause development of anti-drug antibodies (ADA). No clinically significant undesirable effects associated with immunogenicity of eculizumab were seen in the initial clinical development programme.

In initial PNH clinical studies of eculizumab (C04-001 and C04-002), the incidence of ADA was similar between eculizumab and placebo treated patients. These findings were further confirmed in a post-authorisation study specifically designed to evaluate the development of ADA (Study M07-003). No presence of ADA was detected in any of the patients.

Furthermore, completed studies in aHUS, refractory gMG, and NMOSD patients support these findings. In patients with aHUS treated with eculizumab in clinical studies, antibodies to eculizumab were detected in 3/100 (3%) patients; 1/100 (1%) patient had low positive values for neutralising antibodies. In a refractory gMG placebo-controlled study ECU-MG-301, none (0/62) of the eculizumab treated patients showed ADA response during the 26-week active treatment, whereas in a refractory gMG extension study ECU-MG-302, a total of 3/117 (2.6%) overall were positive for ADAs at any post-baseline visit. Positive ADA results appeared to be transient, as positive titres were not observed at subsequent visits, and there were no clinical findings in these patients suggestive of an effect of positive ADA titres. In an NMOSD placebo-controlled study ECU-NMO-301, 2/95 (2.1%) of the eculizumab treated patients showed ADA response post baseline with 2 positive ADA samples of low titre and transient. Both patients were negative for neutralising antibodies. There has been no observed correlation of antibody development to clinical response or adverse events.

The post-marketing surveillance via routine and additional pharmacovigilance activities since the IBD did not identify any new and significant information that would provide evidence of significant undesirable clinical outcomes associated with immunogenicity. No new safety findings arose from the two completed category 3 post-authorisation safety studies with SOLIRIS in patients with PNH (M07-001) and aHUS (M11-001). Both commitments have been considered fulfilled. As of 30 June 2024, the cumulative reporting rate for this risk continue to be low at 0.02 cases per 100 patient-years. The development of ADA was not linked to any clinically significant undesirable outcomes such as adverse reactions or lack of effectiveness.

All therapeutic proteins, including monoclonal antibodies such as eculizumab, may be associated with the development of ADA. However, the nature of these ADA and their clinical consequences differ. The data collected to date do not suggest neutralising nature of ADA and the presence of ADA does not suggest any contributing role or association in development of adverse events, such as various hypersensitivity reactions.

"Aspergillus infection" previously classified as an important identified risk is proposed to be removed from the list of safety concerns, based on the rationale discussed below.

Rationale:

This risk was based on the initial findings from the clinical development programme for eculizumab for prevention of antibody mediated rejection in kidney transplant recipients (Studies C10 001 and C10 002) and post marketing experience. Since host defence against Aspergillus infection is mainly driven by cellular immunity and complement component (C3a, C3b iC3b, and C5a), allowing chemotactism and opsonisation, eculizumab C5 blockade has only a partial effect on the host defence against Aspergillus infections and therefore, has been observed only in severely immunocompromised patients.

In the clinical trials, 3 cases of *Aspergillus* infection were reported in the overall clinical development programme for eculizumab (per the safety database) across all investigated therapeutic areas (ie, not being limited to the indications for use) as of the data lock point of 01 October 2023.

In the post-marketing experience, 80 cases of *Aspergillus* infection were reported from the spontaneous and solicited post-marketing sources as of the data lock point of 01 October 2023, showing a stable cumulative post-marketing reporting rates of 0.09 per 100 patient-years, which is comparable to the rates in patients at risk (ie, severely immunosuppressed individuals) within the general population.

This risk is well characterized and has been sufficiently mitigated through routine risk minimization measures (SmPC, PL etc.). No additional risk minimization measure or pharmacovigilance activities are deemed necessary. This risk will continue to be monitored via routine pharmacovigilance activities.

2.7.3 Details of important identified risks, important potential risks and missing information

2.7.3.1 Presentation of important identified risks and important potential risks

2.7.3.1.1 Important identified risk 1: Meningococcal infections

Potential mechanism(s):

Complement is known to play an important role in host defence against infections (Ram et al 2010). Deficiency of terminal complement components is associated with an increased incidence of infection with *Neisseria* spp., especially *N meningitidis*.

The increased susceptibility to infections caused by *N meningitidis* is directly related to the eculizumab mode of action (inhibition of C5), resulting in deficiency of terminal complement components.

Evidence source(s) and strength of evidence:

This important identified risk is based on the results from the clinical development programme for eculizumab. Eculizumab mode of action is based on terminal complement (C5) inhibition which is associated with an increased incidence of meningococcal infections caused by *N meningitidis*, as meningococcus is primarily cleared by the terminal complement components.

The link between terminal complement components deficiency states and (serious) infections caused by *N meningitidis* is firmly established and evidenced by the scientific literature (Balmer and Miller 2002, Cartwright et al 2001, Figueroa and Densen 1991, Ram et al 2010, Ross and Densen 1984).

Characterisation of the risk:

Cases of meningococcal infections were reported in clinical trials and post-marketing experience with eculizumab with the overall uncommon frequency (ie, ≥ 1/1,000 to < 1/100).

In the clinical trials, 7 cases of meningococcal infections were reported in the overall clinical development programme for eculizumab (per the safety database) across all investigated therapeutic areas (ie, not being limited to the approved indications for use) as of the data lock point of 30 June 2024.

In the post-marketing experience, 231 cases of meningococcal infections were reported from the spontaneous and solicited post-marketing sources as of the data lock point of 30 June 2024, showing a stable cumulative post-marketing reporting rate of 0.26 per 100 patient-years. A comprehensive analysis of the data collected during the post-marketing experience did not change the overall characterisation of this risk, based on the data initially collected in the clinical trials.

Meningococcal infection is usually serious and can quickly become life-threatening or fatal if not recognised early and treated with appropriate antibiotics. Therefore, the impact of these infections on patients' quality of life is significant. Furthermore, meningococcal infections may leave patients with disabling permanent sequelae including physical, neurological, cognitive, behavioural and psychological consequences, such as hearing loss, amputations, spasticity, skin scarring, seizures, and neurodevelopmental deficits (Pace and Pollard 2012, Vyse et al 2013).

Based on the cumulative clinical trial and post-marketing experience data, the majority of meningococcal infections resolved (with or without sequelae) and only infrequently had fatal outcomes. The cumulative reporting rate of fatal meningococcal infections remains stable over the post-marketing experience at 0.03 per 100 patient-years, which is in line with the rates seen in the general population (MacNeil et al 2018, van Deuren et al 2000).

Analysis of available post-marketing data showed that most of the fatal outcomes were a consequence of the delay in diagnosis and/or treatment of infection. Timely diagnosis and treatment initiation immediately after infections presentation has been shown to markedly impact the outcome (Vyse et al 2013).

Risk factors and risk groups:

Main risk factors for these infections include:

- Genetic deficiency or therapeutic inhibition of terminal complement
- Lack of commercially available vaccine against certain meningococcus serogroup
- (Partial) resistance of meningococcal strain to prophylactic antibiotics
- Professionals who are exposed to environments of greater risk for meningococcal disease
- Research, industrial, and clinical laboratory personnel who are routinely exposed to *N meningitidis*
- Military personnel during recruit training (military personnel may be at increased risk of meningococcal infections when accommodated in close quarters)
- Day-care centre workers
- Living on a college or university campus
- Travelling to endemic areas for meningococcal meningitis (eg, India, Sub-Saharan Africa, pilgrimage to Saudi Arabia for Hajj).

No data were identified as additional risk factors for meningococcal infections related to underlying disease such as PNH, aHUS, refractory gMG, or NMOSD.

Preventability:

Eculizumab must not be initiated in patients with unresolved *N meningitidis* infection or in patients who are not currently vaccinated against *N meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.

The occurrence of meningococcal infections can be reduced by means of meningococcal vaccination prior to initiation of eculizumab treatment. However, vaccines are not available against all known serotypes of *N meningitidis* and not all vaccines are available globally. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Refer to Section 5.2 for a detailed description of additional risk minimisation measures for SOLIRIS, designed to prevent and/or minimise this risk.

Impact on the risk-benefit balance of the product:

Meningococcal infection is serious, life-threatening acute condition with potentially fatal outcomes if not recognised in a timely manner and treated. If no preventive measures were established, the impact of this risk on the benefit-risk balance of the product would have been highly unfavourable.

Increased risk of meningococcal infections is directly associated with the eculizumab mode of action, causing deficiency in terminal complement components, and is, therefore, associated with SOLIRIS, with potential impact on the drug's benefit-risk balance.

The long-term post-marketing experience with SOLIRIS showed low and stable overall reporting rates of meningococcal infections in eculizumab-treated patients. Fatalities within eculizumab-treated meningococcal cases occurred at a proportion similar to that reported among meningococcal cases in the general population (MacNeil et al 2018, van Deuren et al 2000). The risk minimisation measures in place to date for the risk of meningococcal infections appear to be appropriate and effective.

Public health impact:

No impact on the public health is expected for this risk.

2.7.3.1.2 Important identified risk 2: Serious infections (including sepsis)

Potential mechanism(s):

Eculizumab mode of action is based on terminal complement (C5) inhibition which is associated with an increased incidence of neisserial infections, as *Neisseria* spp. are primarily cleared by terminal complement components.

The role of terminal complement inhibition in incidence of other serious infections is much lower as eculizumab does not inhibit early complement components which are able to clear most infections other than those caused by *Neisseria* spp.

Evidence source(s) and strength of evidence:

This important identified risk is based on the results from the clinical development programme for eculizumab. Eculizumab mode of action is based on terminal complement (C5) inhibition, impacting in a minor way the ability to clear infections other than *Neisseria* spp. infections in eculizumab-treated patients, potentially leading to serious infections and/or sepsis, even though this impact is significantly lower since early complement components are not affected by eculizumab.

However, scientific literature shows that patients with terminal complement deficiency are only at increased risk of *Neisseria* spp. infections (Figueroa and Densen 1991, Ram et al

2010). Moreover, patients receiving eculizumab are often at increased risk of infection due to the underlying medical condition or its complications.

Characterisation of the risk:

Cases of serious infections (including sepsis) were reported in clinical trials and post-marketing experience with eculizumab with a varying frequency, ranging from common (ie, ≥ 1/100 to < 1/10) to rare (ie, ≥ 1/10,000 to < 1/1,000).

In the clinical trials, 132 cases of serious infections (including sepsis) were reported in the overall clinical development programme for eculizumab (per the safety database) across all investigated therapeutic areas (ie, not being limited to the indications for use) as of the data lock point of 01 October 2023.

In the post-marketing experience, 1,214 cases of serious infections (including sepsis) were reported from the spontaneous and solicited post-marketing sources as of the data lock point of 01 October 2023, showing a stable cumulative post-marketing reporting rate of 7.58 per 100 patient-years. A comprehensive analysis of the data collected during the post-marketing experience did not change the overall characterisation of this risk, based on the data initially collected in the clinical trials.

Infections may become rapidly serious in immunocompromised patients, such as patients with bone marrow disorders, renal failure or those receiving immunosuppressive therapy. Sepsis is usually serious and can quickly become life-threatening or fatal if not recognised early and appropriately treated. The most severe cases of sepsis may require intensive care.

Reversibility and long-term outcomes depend on the nature of infections and characteristics of affected patients. Most of the reports of serious infections associated with eculizumab are confounded by the underlying condition, associated with increased risk of infections, such as bone marrow failure, renal failure with dialysis, diabetes mellitus, or concomitant immunosuppressive therapy.

The experience from the clinical trials and post-marketing experience with eculizumab showed that patients who developed serious infection generally recovered without sequelae with appropriate antibiotic treatment. However, fatal cases were reported in post-marketing setting.

Risk factors and risk groups:

Patients with underlying immunodeficiency or acquired conditions (eg, aplastic anaemia or myelodysplastic syndrome in patients with PNH or ESRD in patients with aHUS) or due to exposure of immunosuppressive drugs (eg, long-term use of corticosteroids and/or

immunosuppressive agents in patients with gMG and NMOSD) are at increased risk of serious infections.

Preventability:

Increased awareness of healthcare professionals (HCPs) and patients about the risk of infection and the related signs and symptoms of serious infection are helpful in minimising the impact of the risk.

Eculizumab should be administered with caution to patients with active systemic infections. It is recommended that patients should seek medical care in case of any signs of infection. Patients at risk of gonorrhoea should test regularly.

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.

Impact on the risk-benefit balance of the product:

Since this risk is directly associated with the mechanism of eculizumab action, it has a significant impact on the benefit-risk balance of SOLIRIS, but acceptable in the light of the anticipated benefits of the therapy and risk minimisation measures in place.

The reported rate of serious infections (including sepsis) has remained stable over the more than 15 years of post-marketing experience with SOLIRIS.

Public health impact:

No impact on the public health is expected for this risk.

2.7.3.1.3 Important identified risk 3: Severe TMA complications due to eculizumab discontinuation in aHUS patients

Potential mechanism(s):

aHUS is a chronic and debilitating life-threatening disease due to life-long uncontrolled complement activation. Eculizumab treatment inhibits this otherwise uncontrolled complement activation. The discontinuation of eculizumab can result in signs and symptoms of severe thrombotic microangiopathy (TMA) complications.

Evidence source(s) and strength of evidence:

This risk resulted from the clinical development programme for eculizumab in aHUS patients. aHUS is a chronic and debilitating life-threatening disease due to life-long uncontrolled complement activation. Eculizumab treatment inhibits this otherwise uncontrolled complement activation. The discontinuation of eculizumab can result in signs and symptoms of severe TMA complications. The efficacy results from C11-003 observational study indicate that patients who discontinued eculizumab experience a higher rate of TMA complications (3-fold) compared to patients who never discontinued eculizumab treatment.

Characterisation of the risk:

Cases of TMA complication have been reported in the setting of missed or delayed SOLIRIS dose in aHUS clinical trials.

During the clinical studies in aHUS patients, the reported severe TMA complications after drug discontinuation included:

- graft failure requiring dialysis
- renal insufficiency
- ESRD
- respiratory distress requiring intubation,
- diarrhoea and increased renal insufficiency
- nephrotic syndrome and renal insufficiency.

These complication were observed as early as 4 weeks and up to 127 weeks following discontinuation of SOLIRIS treatment in some patients. Additional serious medical complications occurred in these patients including severe worsening of kidney function, acute renal transplant rejection, disease-related hospitalisation, and progression to ESRD requiring dialysis. Despite SOLIRIS re-initiation following discontinuation, progression to ESRD occurred in 1 patient.

The long-term outcome may include ESRD in kidney allograft requiring chronic dialysis; ESRD; residual renal insufficiency, or kidney transplant rejection.

Risk factors and risk groups:

Complement dysregulation in patients with aHUS due to genetic abnormalities or acquired deficiencies is associated with TMA (Benz and Amann 2010, Tsai 2006) represent the known risk factors.

Preventability:

Increased awareness of the HCPs and patients about the risk of TMA complications after discontinuation and their related signs and symptoms are helpful in minimising the impact of the risk.

Discontinuation of treatment should only be considered if medically justified.

If aHUS patients discontinue treatment with eculizumab, they should be monitored closely for signs and symptoms of severe TMA complications. However, monitoring may be insufficient to predict or prevent severe TMA complications in patients with aHUS after discontinuation of SOLIRIS.

Impact on the risk-benefit balance of the product:

The impact of this risk on benefit-risk profile of SOLIRIS is acceptable in the light of the anticipated benefits of the therapy and risk minimisation measures in place.

Public health impact:

No impact on the public health is expected for this risk.

2.7.3.1.4 Important identified risk 4: Infusion reactions

Potential mechanism(s):

As with all therapeutic proteins, administration of SOLIRIS may result in infusion reactions and could cause allergic or hypersensitivity reactions.

Evidence source(s) and strength of evidence:

This important identified risk is based on the observations made within the clinical development programme for eculizumab. As with all therapeutic proteins, administration of SOLIRIS may result in infusion reactions and could cause allergic or hypersensitivity reactions. Most of infusion-reactions which occurred in patients receiving eculizumab were non-serious and did not require discontinuation of eculizumab. In the post-marketing setting anaphylactic/anaphylactoid reactions have been reported during or following eculizumab infusion.

In PNH clinical studies, adverse events were documented in the Case Report Form as to whether they occurred within 24 or 48 hours of study medication. According to this definition of infusion reaction, events were generally similar when comparing the eculizumab treated patients from C04-001 and C04-002 (26 weeks) to placebo-treated patients from C04-001.

Characterisation of the risk:

Cases of infusion-related reactions were reported in clinical trials and post-marketing experience with eculizumab with a common frequency (ie, ≥ 1/100 to < 1/10).

In the clinical trials, 15 cases of infusion reaction were reported in the overall clinical development programme for eculizumab (per the safety database) across all investigated therapeutic areas (ie, not being limited to the indications for use) as of the data lock point of 01 October 2023.

In the post-marketing experience, 612 cases of serious infusion reaction were reported from spontaneous and solicited post-marketing sources as of the data lock point of 01 October 2023, showing a stable cumulative post-marketing reporting rates of 0.69 per 100 patient-years. A comprehensive analysis of the data collected during the post-marketing experience did not change the overall characterisation of this risk.

The severity of infusion reaction ranged in clinical trials with eculizumab and post-marketing setting from mild to severe. Immune system disorders within 48 hours of SOLIRIS administration did not differ from placebo treatment in clinical trials with eculizumab.

Most of the infusion reactions in patients receiving eculizumab were non-serious and did not require discontinuation of eculizumab. Anaphylactic/anaphylactoid reactions have been reported in the post-marketing setting during or following eculizumab infusion.

Infusion reactions are fully reversible if recognised early and treated in a timely manner by appropriate measures. No long-term outcomes or impact on quality of life are expected.

Risk factors and risk groups:

Patients with hypersensitivity to eculizumab, murine proteins or to any of the excipients.

No data were identified for the specific risk factors for infusion reactions in patients with PNH, aHUS, refractory gMG, or NMOSD.

Preventability:

Therapy with SOLIRIS must not be initiated in patients with known hypersensitivity to eculizumab, murine proteins or to any of the excipients.

Impact on the risk-benefit balance of the product:

The impact of this risk on benefit-risk profile of SOLIRIS is acceptable in the light of the anticipated benefits of the therapy and risk minimisation measures in place.

Public health impact:

No impact on the public health is expected for this risk.

2.7.3.2 Presentation of the missing information

Not applicable.

2.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

2.8.1 Summary of the safety concerns

Table 2-18 Summary of safety concerns

Important identified risks	Meningococcal infections Serious infections (including sepsis) Severe TMA complications due to drug discontinuation in aHUS patients Infusion reactions
Important potential risks	None
Missing information	None

aHUS, atypical haemolytic uraemic syndrome; TMA, thrombotic microangiopathy.

3 PART III: PHARMACOVIGILANCE PLAN

3.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Specific adverse reaction follow-up questionnaire for meningococcal infections:**

This structured follow-up form is designed to optimise collection of all relevant information associated with the case reports of meningococcal infections to deepen the understanding of the factors leading to this risk associated with eculizumab.

This form collects detailed information about the patient, concerned medicinal product, patient's history with meningococcal infections and information about past vaccination/antibiotic prophylaxis. It further collects information on laboratory findings (bacteriology, serology, biopsy) and clinical presentation of the event. Finally, information about treatment and outcome of the event are collected.

3.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

The pharmacovigilance plan does not include any additional pharmacovigilance activities.

3.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None.

5 PART V: RISK MINIMISATION MEASURES

Risk Minimisation Plan

5.1 ROUTINE RISK MINIMISATION MEASURES

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Meningococcal infections	**Routine risk communication**: SmPC sections 4.3, 4.4, and 4.8 PL sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Vaccination (including the need for antibiotic prophylaxis until 2 weeks after vaccination) is recommended in SmPC section 4.4. Information on educational materials and signs and symptoms of meningococcal infections in included in SmPC section 4.4. Signs and symptoms of meningococcal infections are closely described in PL section 2. **Other routine risk minimisation measures beyond the Product Information**: Restricted medical prescription
Serious infections (including sepsis)	**Routine risk communication**: SmPC sections 4.4 and 4.8 PL sections 2 and 4 **Other routine risk minimisation measures beyond the Product Information**: Restricted medical prescription
Severe TMA complications due to drug discontinuation in aHUS patients	**Routine risk communication**: SmPC section 4.4 PL section 3 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Monitoring of aHUS patients who discontinued SOLIRIS is recommended and further specified in SmPC section 4.4 and PL section 3. **Other routine risk minimisation measures beyond the Product Information**: Restricted medical prescription
Infusion reactions	**Routine risk communication**: SmPC sections 4.2, 4.4, and 4.8

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
	PL sections 2, 3, and 4 **Other routine risk minimisation measures beyond the Product Information**: Restricted medical prescription

aHUS, atypical haemolytic uraemic syndrome; PL, package leaflet; SmPC, summary of product characteristics; TMA, thrombotic microangiopathy

5.2 ADDITIONAL RISK MINIMISATION MEASURES

5.2.1 Educational materials

5.2.1.1 Educational materials for healthcare professionals

5.2.1.1.1 Guide for healthcare professionals

Objectives:

To instruct the HCPs, about the detection, careful monitoring, and proper management of meningococcal infections associated with SOLIRIS.

To educate HCPs about *N meningitidis* vaccines: To instruct HCPs regarding re-vaccination according to manufacturers' direction through product information and national guidelines / recommendations.

To have all patients vaccinated at least 2 weeks prior to receiving SOLIRIS unless the risk of delaying SOLIRIS therapy outweighs the risks of developing a meningococcal infection and re-vaccinated periodically (according to manufacturers' product information and national guidelines / recommendations). Patients that cannot be vaccinated 2 weeks prior to receiving SOLIRIS must receive prophylactic antibiotics before and until 2 weeks after the vaccination.

List of addressed safety concerns:

- Meningococcal infections.

Rationale for the additional risk minimisation activity:

To inform HCPs regarding the risk of meningococcal infection associated with eculizumab treatment, that may lead to a fatal outcome. HCPs must educate their patients to seek immediate medical care as soon as they experience any signs and symptoms of meningococcal infections.

Target audience and planned distribution path:

HCPs using the educational material.

Plans to evaluate the effectiveness of the interventions and criteria for success:
The effectiveness evaluation and criteria for success will be assessment of outcome indicators, ie, rate of meningococcal infection, and will be presented in the PSURs.

5.2.1.2 Educational material for the patients/parents/caregivers

5.2.1.2.1 Guide for patients/parents/caregivers

Objectives:
To educate patients/parents/caregivers about the detection and proper management of selected safety concerns associated with SOLIRIS.

To have all patients vaccinated at least 2 weeks prior to receiving SOLIRIS unless the risk of delaying SOLIRIS therapy outweighs the risks of developing a meningococcal infection and re-vaccinated periodically (according to manufacturers' product information and national guidelines / recommendations). Patients that cannot be vaccinated 2 weeks prior to receiving SOLIRIS must receive prophylactic antibiotics before and until 2 weeks after the vaccination.

To instruct patients/parents/caregivers about the detection of possible meningococcal or general infection and steps to manage based on the product information.

List of addressed safety concerns:

- Meningococcal infections.
- Serious infections (including sepsis)
- Severe TMA complications due to discontinuation in aHUS patients

Rationale for the additional risk minimisation activity:
To inform patients/parents/caregivers about the main risks associated with eculizumab treatment, especially the risk of meningococcal infections associated with eculizumab treatment that may lead to a fatal outcome. Patients/parents/caregivers must be trained to seek immediate medical care as soon as they experience any signs and symptoms of meningococcal infections and to carry and show their safety card at all times.

Target audience and planned distribution path:

- Patients
- Physicians other than usual prescribers
- Parents, caregivers, and other child carers (e.g. school, day care services or persons, etc.)

Plans to evaluate the effectiveness of the interventions and criteria for success:
The effectiveness evaluation and criteria for success will be assessment of outcome indicators, ie, rate of meningococcal infection, and will be presented in the PSURs.

5.2.1.2.2 Patient card

Objectives:

To list signs and symptoms of meningococcal infections to help the patients/parents/caregivers to identify potential meningococcal infection and to seek immediately medical care. In addition, when patients present to a physician different than the usual prescriber, it helps to promptly identify potential meningococcal infections and to initiate appropriate antibiotic treatment.

List of addressed safety concerns:

- Meningococcal infections
- Serious infections (including sepsis)

Rationale for the additional risk minimisation activity:

Signs and symptoms of meningococcal infections need to be recognised in a timely manner. This card highlights these signs and symptoms as well as the need for seeking immediate medical attention if they occur. This card also emphasises that the patient must receive vaccination or revaccination according to current national vaccination guidelines for vaccination use.

Target audience and planned distribution path:

- Patients/parents/caregivers.
- Physicians other than usual prescribers.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness evaluation and criteria for success will be assessment of outcome indicators, ie, rate of meningococcal infection, and will be presented in the PSURs.

5.2.2 Annual vaccination reminders for HCPs

Objectives:

To remind the HCPs on an annual basis to verify and ensure that the patient's vaccination against meningococcal infections are still current according to local vaccination guideline.

List of addressed safety concerns:

- Meningococcal infections.

Rationale for the additional risk minimisation activity:

To highlight the importance of an effective vaccination against meningococcal infections to minimise this important risk.

Target audience and planned distribution path:

Prescribers or pharmacists who prescribe/dispense eculizumab

Plans to evaluate the effectiveness of the interventions and criteria for success:

The MAH ensures the reminder is sent annually to the HCPs.

Removal of additional risk minimisation activity – controlled distribution

Rationale for the removal:

The additional risk minimisation measures have been revised as described in Section 5.2 and the controlled distribution measure, previously in place since the initial marketing authorisation in the EU has been removed.

Based on the cumulative analysis of cases of meningococcal infections, the evaluation of the current additional risk minimisation measures (process indicators such as knowledge and understanding of the risk by the HCPs and outcome indicators such as rates of meningococcal infections over time), the evidence that vaccination guidance for complement inhibitors has become a standard healthcare practice and the evaluation of the unintended outcomes, the initially implemented additional risk minimisation measures, which included controlled distribution as one of the measures, have been revised.

The revised additional risk minimisation measurers will continue to use the educational materials focusing on addressing the risk of meningococcal infections and removal of other safety concerns given that some of these risks are well known by the HCPs.

The educational tools for HCPs will continue to include a guide for HCPs. The educational tools for patients will continue to include a guide for patients/parents/caregivers and a patient card. The annual vaccination reminders will be continued to be sent to HCPs.

5.3 SUMMARY OF RISK MINIMISATION MEASURES

Table 5-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Meningococcal infections	**Routine risk minimisation measures**: SmPC sections 4.3, 4.4, and 4.8 PL sections 2 and 4 Recommendations for vaccination/antibiotic prophylaxis in SmPC section 4.4 Signs and symptoms of meningococcal infections listed in SmPC section 4.4 and PL section 2 Restricted medical prescription **Additional risk minimisation measures**: Educational materials Guide for healthcare professionals Guide for patients/parents/caregivers Patient card Annual vaccination reminder	**Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting:** Specific adverse reaction follow-up questionnaire **Additional pharmacovigilance activities** None
Serious infections (including sepsis)	**Routine risk minimisation measures**: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription **Additional risk minimisation measures**: Guide for patients/parents/caregivers Patient card	None

Table 5-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Severe TMA complications due to drug discontinuation in aHUS patients	**Routine risk minimisation measures**: SmPC section 4.4 PL section 3 Monitoring of patients who discontinued SOLIRIS recommended in SmPC section 4.4 and PL section 3 Restricted medical prescription **Additional risk minimisation measures**: Guide for patients/parents/caregivers	None
Infusion reactions	**Routine risk minimisation measures**: SmPC sections 4.2, 4.4, and 4.8 PL sections 2, 3, and 4 Restricted medical prescription **Additional risk minimisation measures**: None	None

aHUS, atypical haemolytic uraemic syndrome; PL, Package Leaflet; SmPC, Summary of Product Characteristics; TMA, thrombotic microangiopathy.

6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for SOLIRIS (eculizumab)

This is a summary of the risk management plan (RMP) for SOLIRIS. The RMP details important risks of SOLIRIS, how these risks can be minimised, and how more information will be obtained about SOLIRIS's risks and uncertainties (missing information).

SOLIRIS's summary of product characteristics (SmPC) of SOLIRIS and its package leaflet give essential information to healthcare professionals and patients on how SOLIRIS should be used.

This summary of the RMP for SOLIRIS should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of SOLIRIS's RMP.

6.1 THE MEDICINE AND WHAT IT IS USED FOR

SOLIRIS is authorised for paroxysmal nocturnal haemoglobinuria (PNH), atypical haemolytic uremic syndrome (aHUS), refractory generalised myasthenia gravis (gMG), and relapsing neuromyelitis optica spectrum disease (NMOSD) (see SmPC for the full indications). It contains eculizumab as the active substance and it is given by intravenous route of administration.

Further information about the evaluation of benefits can be found in EPAR of SOLIRIS, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

6.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of SOLIRIS, together with measures to minimise such risks and the proposed studies for learning more about SOLIRIS's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In the case of SOLIRIS, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

6.2.1 List of important risks and missing information

Important risks of SOLIRIS are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SOLIRIS. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 6-1 List of important risks and missing information

Important identified risks	Meningococcal infections Serious infections (including sepsis) Severe TMA complications due to drug discontinuation in aHUS patients Infusion reactions
Important potential risks	None
Missing Information	None

aHUS, atypical haemolytic uraemic syndrome; TMA, thrombotic microangiopathy.

6.2.2 Summary of important risks

Table 6-2 Identified risk of meningococcal infections

Evidence for linking the risk to the medicine	This important identified risk is based on the results from the clinical development programme for eculizumab. Eculizumab mode of action is based on terminal complement (C5) inhibition which is associated with an increased incidence of meningococcal infections caused by *N meningitidis*, as meningococcus is primarily cleared by the terminal complement components. The link between terminal complement components deficiency states and (serious) infections caused by *N meningitidis* is firmly established and evidenced by the scientific literature (Balmer and Miller 2002, Cartwright et al 2001, Figueroa and Densen 1991, Ram et al 2010, Ross and Densen 1984).
Risk factors and risk groups	Main risk factors for these infections include: • Genetic deficiency or therapeutic inhibition of terminal complement • Lack of commercially available vaccine against certain meningococcus serogroup • (Partial) resistance of meningococcal strain to prophylactic antibiotics • Professionals who are exposed to environments of greater risk for meningococcal disease • Research, industrial, and clinical laboratory personnel who are routinely exposed to *N meningitidis* • Military personnel during recruit training (military personnel may be at increased risk of meningococcal infections when accommodated in close quarters) • Day care centre workers • Living on a college or university campus • Travelling to endemic areas for meningococcal meningitis (eg, India, Sub Saharan Africa, pilgrimage to Saudi Arabia for Hajj). No data were identified as additional risk factors for meningococcal infections related to underlying disease such as PNH, aHUS, refractory gMG, or NMOSD.

Table 6-2 Identified risk of meningococcal infections

Risk minimisation measures	**Routine risk minimisation measures**: SmPC sections 4.3, 4.4, and 4.8 PL sections 2 and 4 Recommendations for vaccination/antibiotic prophylaxis in SmPC section 4.4 Signs and symptoms of meningococcal infections listed in SmPC section 4.4 and PL section 2 Restricted medical prescription **Additional risk minimisation measures**: Educational materials Guide for healthcare professionals Guide for patients/parents/caregivers Patient card Annual vaccination reminder

aHUS, atypical haemolytic uremic syndrome; C5, complement component 5; gMG, generalised myasthenia gravis; NMOSD, neuromyelitis optica spectrum disorder; PL, Package Leaflet; PNH, paroxysmal nocturnal haemoglobinuria; SmPC, Summary of Product Characteristics.

Balmer P and Miller E. Meningococcal disease: how to prevent and how to manage. Curr Opin Infect Dis. 2002; 15(3):275-281.

Cartwright K, Noah N, Peltola H. Meningococcal disease in Europe: epidemiology, mortality, and prevention with conjugate vaccines. Report of a European advisory board meeting Vienna, Austria, 6-8 October, 2000. Vaccine. 2001; 19(31):4347-4356.

Figueroa JE and Densen P. Infectious diseases associated with complement deficiencies. Clin Microbiol Rev. 1991; 4(3):359-395.

Ram S, Lewis LA, Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. Clin Microbiol Rev. 2010; 23(4):740-780.

Ross SC and Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. Medicine (Baltimore). 1984; 63(5):243-273.

Table 6-3 Identified risk of serious infections (including sepsis)

Evidence for linking the risk to the medicine	This important identified risk is based on the results from the clinical development programme for eculizumab. Eculizumab mode of action is based on terminal complement (C5) inhibition, impacting in a minor way the ability to clear infections other than *Neisseria* spp. infections in eculizumab treated patients, potentially leading to serious infections and/or sepsis, even though this impact is significantly lower since early complement components are not affected by eculizumab. However, scientific literature shows that patients with terminal complement deficiency are only at increased risk of *Neisseria* spp. infections (Figueroa and Densen 1991, Ram et al 2010). Moreover, patients receiving eculizumab are often at increased risk of infection due to the underlying medical condition or its complications.
Risk factors and risk groups	Patients with underlying immunodeficiency or acquired conditions (eg, aplastic anaemia or myelodysplastic syndrome in patients with PNH or end-stage renal disease in patients with aHUS) or due to exposure of immunosuppressive drugs (eg, long-term use of corticosteroids and/or immunosuppressive agents in patients with gMG and NMOSD) are at increased risk of serious infections.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription **Additional risk minimisation measures**: Guide for patients/parents/caregivers Patient card

aHUS, atypical haemolytic uremic syndrome; C5, complement component 5; gMG, generalised myasthenia gravis; NMOSD, neuromyelitis optica spectrum disorder; PL, Package Leaflet; PNH, paroxysmal nocturnal haemoglobinuria; SmPC, Summary of Product Characteristics.

Figueroa JE and Densen P. Infectious diseases associated with complement deficiencies. Clin Microbiol Rev. 1991; 4(3):359-395.

Ram S, Lewis LA, Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. Clin Microbiol Rev. 2010; 23(4):740-780.

Table 6-4 Identified risk of severe TMA complications due to drug discontinuation in aHUS patients

Evidence for linking the risk to the medicine	This risk resulted from the clinical development programme for eculizumab in aHUS patients. aHUS is a chronic and debilitating life threatening disease due to life-long uncontrolled complement activation. Eculizumab treatment inhibits this otherwise uncontrolled complement activation. The discontinuation of eculizumab can result in signs and symptoms of severe TMA complications. The efficacy results from C11-003 observational study indicate that patients who discontinued eculizumab experience a higher rate of TMA complications (3-fold) compared to patients who never discontinued eculizumab treatment.
Risk factors and risk groups	Complement dysregulation in patients with aHUS due to genetic abnormalities or acquired deficiencies is associated with TMA (Benz and Amann 2010, Tsai 2006) represent known risk factors.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section 4.4 PL section 3 Monitoring of patients who discontinued SOLIRIS recommended in SmPC section 4.4 and PL section 3 Restricted medical prescription **Additional risk minimisation measures**: Guide for patients/parents/caregivers

aHUS, atypical haemolytic uremic syndrome; PL, Package Leaflet; SmPC, Summary of Product Characteristics; TMA, thrombotic microangiopathy.

Benz K and Amann K. Thrombotic microangiopathy: new insights. Current opinion in nephrology and hypertension. 2010; 19(3):242-247.

Tsai H-M. The molecular biology of thrombotic microangiopathy. Kidney international. 2006; 70(1):16-23.

Table 6-5 Identified risk of infusion reactions

Evidence for linking the risk to the medicine	This important identified risk is based on the observations made within the clinical development programme for eculizumab. As with all therapeutic proteins, administration of SOLIRIS may result in infusion reactions and could cause allergic or hypersensitivity reactions. Most of infusion-reactions which occurred in patients receiving eculizumab were non-serious and did not require discontinuation of eculizumab. In the post marketing setting anaphylactic/anaphylactoid reactions have been reported during or following eculizumab infusion. In PNH clinical studies, adverse events were documented in the Case Report Form as to whether they occurred within 24 or 48 hours of study medication. According to this definition of infusion reaction, events were generally similar when comparing the eculizumab treated patients from C04-001 and C04-002 (26 weeks) to placebo-treated patients from C04-001.
Risk factors and risk groups	Patients with hypersensitivity to eculizumab, murine proteins or to any of the excipients. No data were identified for the specific risk factors for infusion reactions in patients with PNH, aHUS, refractory gMG, or NMOSD.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, and 4.8 PL sections 2, 3, and 4 Restricted medical prescription **Additional risk minimisation measures:** None

aHUS, atypical haemolytic uremic syndrome; gMG, generalised myasthenia gravis; NMOSD, neuromyelitis optica spectrum disorder; PL, Package Leaflet; PNH, paroxysmal nocturnal haemoglobinuria; SmPC, Summary of Product Characteristics.

6.2.3 Post-authorisation development plan

6.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of SOLIRIS.

6.2.3.2 Other studies in post-authorisation development plan

There are no studies required for SOLIRIS.

7 PART VII: ANNEXES

7.1 ANNEX 4: Specific adverse drug reaction follow-up forms

- *Global Pharmacovigilance Suspected/Confirmed Meningococcal Case Questionnaire*

7.2 ANNEX 6: Details of proposed additional risk minimisation activities

7.2.1 Approved key messages of the additional risk minimisation measure

7.2.1.1 Educational materials for healthcare professionals

- The Summary of Product Characteristics
- Guide for healthcare professionals

Guide for healthcare professionals

- Treatment with eculizumab increases the risk of severe infection and sepsis, especially of *Neisseria meningitidis* and other *Neisseria species*, including disseminated gonorrhoeae.
- All patients must be monitored for signs of meningococcal infection.
- The need for patients to be vaccinated against Neisseria meningitidis 2 weeks prior to receiving eculizumab and to receive antibiotic prophylaxis.

- Patients must be vaccinated and revaccinated according to current national guidelines for vaccination use.
- The need to explain to and ensure understanding of by patients/parents/carers:
  - the risks of treatment with eculizumab
  - the signs and symptoms of sepsis/severe infection and what action to take
  - the patient/parent/carer's guides and their contents
  - the need to carry the patient card and to tell any healthcare practitioner that he/she is receiving treatment with eculizumab
  - the requirement for vaccinations, antibiotic prophylaxis and revaccination according to current national guidelines for vaccination use.

7.2.1.2 Educational materials for patients/parents/caregivers

- Patient Information Leaflet
- Guide for patient/parent/caregiver
- Patient card

Guide for patient/parent/caregiver

- Treatment with eculizumab increases the risk of severe infection, especially, *Neisseria meningitidis* and other *Neisseria species,* including disseminated gonorrhoeae.
- Signs and symptoms of severe infection and the need to obtain urgent medical care.
- The patient 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 patient must be vaccinated and revaccinated according to current national guidelines for vaccination use.
- The need for children to be vaccinated against pneumococcus and *Haemophilus influenzae* before eculizumab treatment.
- 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.

Patient card

- Signs and symptoms of infection and sepsis.
- Warning to seek immediate medical care if above are present.

- Statement that the patient is receiving eculizumab
- Statement that the patient must receive vaccination and revaccination according to current national vaccination guidelines for vaccination use. The vaccination and re-vaccination dates should be included on the patient card.
- Contact details where a healthcare practitioner can receive further information.

7.2.1.3 Annual vaccination reminders for HCPs

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.

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Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire

Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347
or clinicalsae@alexion.com (for clinical trials only)

Alexion Manufacturer Number:

Date of Birth: *(DD/MMM/YYYY)*

Age (if known):

Or Age Category:

☐ Child (<12 years) ☐ Adolescent (12-17 years) ☐ Adults (18-65 years) ☐ Elderly (>65 years)

Gender:

☐ Female ☐ Male ☐ Prefer not to disclose

☐ Intersex ☐ Transgender

Weight: ☐ lbs. ☐ kgs.

Height: ☐ cm. ☐ in.

Ethnicity: *(Applicable for US Only. Record only if obtained through voluntary self-identification.)*

☐ Not Hispanic or Latino ☐ Hispanic or Latino

☐ Not Reported ☐ Unknown

Race: *(Applicable for US Only. Record only if obtained through voluntary self-identification.)*

☐ Aboriginal or Torres Strait Islander ☐ Caucasian

☐ African American ☐ Native Hawaiian or Pacific Islander

☐ American Indian or Alaska Native ☐ Not Reported

☐ Asian ☐ Unknown

☐ Black

☐ Other *(Specify)*

Product Name: **Current Dosage:**

Initiation Date and Dosage: **Last dose prior to the event Date and Dosage:** *(DD/MMM/YYYY)*

Action Taken with Product:

☐ No Change ☐ Temporarily withdrawn ☐ Drug Interrupted ☐ Withdrawn

☐ Dose Increased ☐ Dose Decreased ☐ Unknown ☐ Not Applicable

☐ Other *(Specify)*

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Product Name: **Current Dosage:**

Initiation Date and Dosage: **Last dose prior to the event Date and Dosage:**
(DD/MMM/YYYY)

Action Taken with Product:

☐ No Change ☐ Temporarily withdrawn ☐ Drug Interrupted ☐ Withdrawn

☐ Dose Increased ☐ Dose Decreased ☐ Unknown ☐ Not Applicable

☐ Other *(Specify)*

Patient History

Previous history of meningococcal infection? ☐ Yes ☐ No ☐ Unknown
(please describe)

Risk factor for meningococcal infection? ☐ Yes ☐ No ☐ Unknown
(please describe)

(e.g., Medical condition, exposure to laboratory, industry, close quarters, college campus, daycare workers, military, living in proximity or recent travel to endemic areas)

Meningococcal Vaccination ☐ Yes *(provide vaccine name and date below)* ☐ No ☐ Unknown

Was the patient vaccinated per Advisory Committee on Immunization Practices (ACIP) guidelines?
(Applicable for US only)

☐ Yes ☐ No ☐ Unknown

Was the patient vaccinated according to current national vaccination guidelines?
(Applicable for ex-US only)

☐ Yes ☐ No ☐ Unknown ☐ Not Applicable

Vaccine Name: ☐ Initial Vaccination date:
(DD/MMM/YYYY)

☐ Booster Vaccination date:

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Vaccine Name: ☐ Initial Vaccination date: *(DD/MMM/YYYY)*

☐ Booster Vaccination date: *(DD/MMM/YYYY)*

Vaccine Name: ☐ Initial Vaccination date: *(DD/MMM/YYYY)*

☐ Booster Vaccination date: *(DD/MMM/YYYY)*

Vaccine Name: ☐ Initial Vaccination date: *(DD/MMM/YYYY)*

☐ Booster Vaccination date: *(DD/MMM/YYYY)*

Antibiotic prophylaxis: ☐ Yes ☐ No

(If yes) Antibiotic Name / Active substance: Dosage / frequency:

Start date: *(DD/MMM/YYYY)* Stop date: *(DD/MMM/YYYY)* ☐ Ongoing

Is the patient compliant with their antibiotic prophylaxis? ☐ Yes ☐ No ☐ Unknown

Bacteriological work up

CSF: *Direct Exam Results:*

CSF: *Culture Results:*

CSF: *PCR Results:*

Blood: *Direct Exam Results:*

Blood: *Culture Results:*

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Blood: *PCR Results:*

Clinical Presentation

Description of initial clinical signs and/or symptoms patient has presented with:

Onset Date of first symptom(s) *(DD/MMM/YYYY)*

Malaise ☐ Yes ☐ No

Myalgia ☐ Yes ☐ No

Fever ☐ Yes ☐ No *(If yes, please provide temp)*

Hypothermia ☐ Yes ☐ No *(If yes, please provide temp)*

Headache ☐ Yes ☐ No

Neck stiffness ☐ Yes ☐ No

Photophobia ☐ Yes ☐ No

Vomiting ☐ Yes ☐ No

Confusion ☐ Yes ☐ No

Chills ☐ Yes ☐ No

Convulsions ☐ Yes ☐ No

Rash ☐ Yes ☐ No *(If yes, please specify type and localization)*

Other ☐ Yes ☐ No *(Please specify)*

Patients who receive(d) Antibiotic Prophylaxis Only:
Minimum Inhibitory Concentration (MIC):

Serology

Neisseria meningitidis serogroup / serotype:

☐ A ☐ B ☐ C ☐ W135 ☐ X ☐ Y ☐ Z

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Other:

(specify)

Neisseria meningitidis serosubtype:
(if available)

Neisseria meningitidis Genotyping (MLST):
(if available)

Meningococcal Antigen Typing System (MATS) assay (For serogroup B infection in patients vaccinated by 4CMenB):

Skin biopsy culture:

☐ Done
☐ Not done

If done, results:

Treatment of the event

Antibiotic Name:

Start date: *(DD/MMM/YYYY)*

Stop date: *(DD/MMM/YYYY)*

☐ Ongoing

Other medication:

Medication Name:

Start date: *(DD/MMM/YYYY)*

Stop date: *(DD/MMM/YYYY)*

☐ Ongoing

Other supportive treatment:

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Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347
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Was the patient admitted to the ICU? ☐ Yes ☐ No ☐ Unknown

Did the patient experience or require any of the following (select all that apply):

☐ Any organ system failure *(specify)*

☐ Mechanical ventilation

☐ Medication (vasopressors) to support blood pressure *(specify)*

Outcome

☐ Unknown

☐ Recovered ☐ Recovered with sequelae *(specify sequelae)*

Date Recovered: (DD/MMM/YYYY)

☐ Ongoing ☐ Fatal *(Specify cause of death)*

Date of Death: (DD/MMM/YYYY)

Additional Comments:

Name of Individual Completing the Form
Designation
Contact Information
Date Form Completed

Signature Page for VV-PVG-001978 v2.0

Approval	Anne Lappereau-Gallot Other 10-Apr-2025 15:49:36 GMT+0000

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