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Soliris concentrate for solution for infusion
Swissmedic Authorisation Number: 59282

Swiss Summary of the Risk Management Plan for Soliris® (Eculizumab)

Based on EU-RMP version number:	20.3
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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of **Soliris** is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of **Soliris** in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. **Alexion Pharma GmbH** is fully responsible for the accuracy and correctness of the content of the published summary RMP of **Soliris**.

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 risks and uncertainties (missing information) of Soliris.

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 the RMP of Soliris.

I. 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.

II. 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 the risks of Soliris, 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 (e.g. 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.

II.A 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).

List of important risks and missing information	
Important identified risks	Meningococcal infections Serious infections (including sepsis) *Aspergillus* infection Severe TMA complications due to drug discontinuation in aHUS patients Infusion reactions
Important potential risks	Serious haemolysis after drug discontinuation in PNH patients Immunogenicity
Missing information	None

II.B Summary of important risks

Identified risk: 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 component 5 (C5) inhibition which is associated with an increased incidence of meningococcal infections caused by *Neisseria 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.

Identified risk: Meningococcal infections	
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 infection when accommodated in close quarters) – Day-care centre workers – Living on a college or university campus – Travelling to endemic areas for meningococcal meningitis (e.g. 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.
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 – Physician's guides (PNH, aHUS, refractory gMG, NMOSD) – Patient's information brochure (PNH, aHUS, refractory gMG, NMOSD) – Parent's information brochure (PNH, aHUS, refractory gMG) – Patient safety card Controlled distribution Vaccination reminder

Identified risk: Meningococcal infections	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: aHUS registry (M11-001) See section II.C of this summary for an overview of the post-authorisation development plan.

Identified risk: 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 also 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. 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 (e.g. 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 (e.g. 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: Educational materials – Physician's guides (PNH, aHUS, refractory gMG, NMOSD) – Patient's information brochure (PNH, aHUS, refractory gMG, NMOSD) – Parent's information brochure (PNH, aHUS, refractory gMG) – Patient safety card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: aHUS registry (M11-001) See section II.C of this summary for an overview of the post-authorisation development plan.

Identified risk: *Aspergillus* infection	
Evidence for linking the risk to the medicine	This important identified risk is 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. Further evidence linking aspergillosis to immunocompromised states is provided in the scientific literature.
Risk factors and risk groups	Underlying severe immunodeficiency condition, acquired or due to other immunosuppressive drugs including steroids, exposure to construction or demolition, severe pancytopenia due to aplastic anaemia, and pre-existing lung impairment or pre-existing *Aspergillus* infection. No data were identified for risk factors for *Aspergillus* or other fungal infections in patients with refractory gMG; however, as refractory gMG patients are on immunosuppressive drugs including steroids and may also have diabetes mellitus, they are potentially at risk. Patients with NMOSD are also treated with various immunosuppressive agents (including intravenous high-dose methylprednisolone for acute attacks and oral corticosteroids, mycophenolate mofetil or azathioprine for prevention of attacks) and may be more prone to opportunistic infections caused by *Aspergillus*.
Risk minimisation measures	Routine risk minimisation measures: – SmPC sections 4.4 and 4.8 – PL section 4 Restricted medical prescription Additional risk minimisation measures: Educational materials – Physician's guides (PNH, aHUS, refractory gMG, NMOSD)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: aHUS registry (M11-001) See section II.C of this summary for an overview of the post-authorisation development plan.

Identified risk: 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

Identified risk: Severe TMA complications due to drug discontinuation in aHUS patients	
	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 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: Educational materials – Physician's guide (aHUS) – Patient's/Parent's information brochure (aHUS)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: aHUS registry (M11-001) See section II.C of this summary for an overview of the post-authorisation development plan.

Identified risk: 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 required 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.

Identified risk: Infusion reactions	
	No data were identified for the 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: Educational materials – Physician's guides (PNH, aHUS, refractory gMG, NMOSD) – Patient's information brochure (PNH, aHUS, refractory gMG, NMOSD) – Parent's information brochure (PNH, aHUS, refractory gMG)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: aHUS registry (M11-001) See section II.C of this summary for an overview of the post-authorisation development plan.

Potential risk: Serious haemolysis after drug discontinuation in PNH patients	
Evidence for linking the risk to the medicine	This potential risk is a theoretical possibility in PNH patients, based on the mode of eculizumab action and nature of PNH.
Risk factors and risk groups	No data were identified for risk factors for serious haemolysis due to drug discontinuation in patients with PNH.
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: Educational materials – Physician's guide (PNH) – Patient's/Parent's information brochure (PNH) – Parent's information brochure (PNH)

Potential risk: Immunogenicity	
Evidence for linking the risk to the medicine	This potential risk is based on the known potential of all medicinal products and on the class effect of all therapeutic proteins, including monoclonal antibodies.
Risk factors and risk groups	No risk factors or risk groups have been identified.
Risk minimisation measures	Routine risk minimisation measures: – SmPC sections 4.4 and 4.8 – PL section 2 Restricted medical prescription Additional risk minimisation measures: Educational materials – Physician's guides (PNH, aHUS, refractory gMG, NMOSD)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: aHUS registry (M11-001) See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.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.

II.C.2 Other studies in post-authorisation development plan

M11-001: "Atypical Hemolytic Uremic Syndrome (aHUS) Registry"

Purpose of the study: The registry aims to collect and evaluate safety and effectiveness data specific to the use of eculizumab in aHUS patients and to assess the long-term manifestations of TMA complications of aHUS as well as other clinical outcomes, including mortality and morbidity in aHUS patients receiving eculizumab treatment or other disease management.