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Ultomiris concentrate for solution for infusion
Swissmedic Authorisation Number: 67278

Swiss Summary of the Risk Management Plan for Ultomiris® (Ravulizumab)

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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 **Ultomiris** 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 **Ultomiris** 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 **Ultomiris**.

PART VI: Summary of the Risk Management Plan

Summary of risk management plan for Ultomiris (ravulizumab)

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

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

This summary of the RMP for Ultomiris 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 for Ultomiris.

I. The medicine and what it is used for

Ultomiris is authorised for treatment of paroxysmal nocturnal haemoglobinuria (PNH), atypical haemolytic uraemic syndrome (aHUS), and generalised myasthenia gravis (gMG) (see SmPC for the full indication). It contains ravulizumab as the active substance and it is given by the intravenous route of administration.

Further information about the evaluation of benefits of Ultomiris can be found in the EPAR for Ultomiris, 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 Ultomiris, together with measures to minimise such risks and the proposed studies for learning more about the risks of Ultomiris, 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 Ultomiris, 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.

If important information that may affect the safe use of Ultomiris is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Ultomiris 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 Ultomiris. 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 infection
Important potential risks	Serious haemolysis after drug discontinuation in PNH patients Severe TMA complications in aHUS patients after ravulizumab discontinuation Immunogenicity Serious infections Malignancies and haematologic abnormalities in PNH patients
Missing information	Use in pregnant and breast-feeding women

II.B Summary of important risks

Identified risk: Meningococcal infection	
Evidence for linking the risk to the medicine	This important identified risk is based on the ravulizumab mode of action, findings from the clinical trial development programme for ravulizumab, and on the long-term experience with eculizumab (Soliris). The link between terminal complement components deficiency states and (serious) infections caused by *N. meningitidis* is firmly established and evidenced by the scientific literature.

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)
Risk minimisation measures	<u>Routine risk minimisation measures</u> – SmPC sections 4.3, 4.4, and 4.8 – PL sections 2 and 4 Recommendations for vaccination/antibiotic prophylaxis in SmPC section 4.4 and PL section 2 Signs and symptoms of meningococcal infections listed in SmPC section 4.4 and PL section 2 Restricted medical prescription <u>Additional risk minimisation measures</u> Educational materials – PNH/aHUS/gMG Physician's Guide – PNH/aHUS/gMG Patient's Information Brochure – PNH/aHUS Parent's Information Brochure – Patient card Controlled distribution Revaccination reminder

Additional pharmacovigilance activities	Additional pharmacovigilance activities: – Study ALXN1210-PNH-301 – Study ALXN1210-PNH-302 – PNH registry (M07-001) – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 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 is a theoretical possibility based on the mode of action of ravulizumab, nature of PNH, and experience with the use (and discontinuation) of Soliris (eculizumab).
Risk factors and risk groups	No risk factors have yet been identified.
Risk minimisation measures	Routine risk minimisation measures – SmPC section 4.4 – PL section 3 Monitoring of patients who discontinued Ultomiris recommended in SmPC section 4.4 and PL section 3 Additional risk minimisation measures Educational materials – PNH Physician's Guide – PNH Patient's Information Brochure – PNH Parent's Information Brochure
Additional pharmacovigilance activities	Additional pharmacovigilance activities: – Study ALXN-1210-PNH-301 – Study ALXN1210-PNH-302 – PNH registry (M07-001) See section II.C of this summary for an overview of the post-authorisation development plan.

Potential risk: Severe TMA complications in aHUS patients after ravulizumab discontinuation	
Evidence for linking the risk to the medicine	This potential risk is based on the long-term observational prospective study with eculizumab (Study C11-003). Discontinuation of eculizumab can result in signs and symptoms of severe TMA complications. The efficacy results from C11-003 observational study with eculizumab indicate that

	patients who discontinued eculizumab experienced a higher rate of TMA recurrence (13.5-fold) and showed a trend toward reduced renal function compared to patients who continued eculizumab treatment. No such effects have been observed in the clinical development programme for ravulizumab in aHUS patients. Therefore, this represents a potential risk for ULTOMIRIS.
Risk factors and risk groups	Patients with known genetic abnormalities in complement genes or known autoantibodies to complement proteins are likely at higher risk.
Risk minimisation measures	Routine risk minimisation measures – SmPC section 4.4 Additional risk minimisation measures Educational materials – aHUS Physician's Guide – aHUS Patient's Information Brochure – aHUS Parent's Information Brochure
Additional pharmacovigilance activities	Additional pharmacovigilance activities: – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 See section II.C of this summary for an overview of the post-authorisation development plan.

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 mAbs.
Risk factors and risk groups	No specific risk factors for the development of immunogenicity have yet been identified.
Risk minimisation measures	Routine risk minimisation measures – SmPC sections 4.4 and 4.8 Additional risk minimisation measures Educational materials – PNH/aHUS/gMG Physician's Guide – PNH/aHUS/gMG Patient's Information Brochure – PNH/aHUS Parent's Information Brochure

Additional pharmacovigilance activities	Additional pharmacovigilance activities: – Study ALXN1210-PNH-301 – Study ALXN1210-PNH-302 – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 See section II.C of this summary for an overview of the post-authorisation development plan.

Potential risk: Serious infections	
Evidence for linking the risk to the medicine	This risk is a based on the mode of action of ravulizumab and experience with the use Soliris (eculizumab). Since relevance of serious infections to ravulizumab therapy has not been confirmed in clinical trials, this remains a potential risk.
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).
Risk minimisation measures	Routine risk minimisation measures – SmPC sections 4.3, 4.4 and 4.8 – PL sections 2, 3 and 4 Recommendations for vaccination of paediatric patients against *Haemophilus influenzae* and pneumococcal infections in SmPC section 4.4 and PL section 2. Additional risk minimisation measures Educational materials – PNH/aHUS/gMG Physician's Guide – PNH/aHUS/gMG Patient's Information Brochure – PNH/aHUS Parent's Information Brochure
Additional pharmacovigilance activities	Additional pharmacovigilance activities: – Study ALXN1210-PNH-301 – Study ALXN1210-PNH-302 – PNH registry (M07-001) – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 See section II.C of this summary for an overview of the post-authorisation development plan.

Potential risk: Malignancies and haematologic abnormalities in PNH patients	
Evidence for linking the risk to the medicine	This potential risk is based on the incidence of malignancies in PNH patients treated by Soliris (eculizumab). As the natural evolution of PNH makes PNH patients more prone to development of haematologic abnormalities or malignancies, the role of eculizumab or ravulizumab remains unknown.
Risk factors and risk groups	Patients with underlying myelodysplastic syndrome or other pre-leukaemic syndromes are at-risk of leukaemia acutisation.
Risk minimisation measures	Routine risk minimisation measures None proposed Additional risk minimisation measures: – PNH Physician's Guide – PNH Patient's Information Brochure – PNH Parent's Information Brochure
Additional pharmacovigilance activities	Additional pharmacovigilance activities: – Study ALXN-1210-PNH-301 – Study ALXN1210-PNH-302 – PNH registry (M07-001) See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Use in pregnant and breast-feeding women	
Risk minimisation measures	Routine risk minimisation measures – SmPC sections 4.6 and 5.3 – PL section 2 Recommendations on contraception in SmPC section 4.8 and PL section 2 Additional risk minimisation measures Educational materials – PNH/aHUS/gMG Physician's Guide – PNH/aHUS/gMG Patient's Information Brochure

Additional pharmacovigilance activities	Additional pharmacovigilance activities: – Study ALXN1210-PNH-301 – Study ALXN1210-PNH-302 – PNH registry (M07-001) – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 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 Ultomiris.

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

ALXN1210-PNH-301

Purpose of the study: This Phase 3 study aims to evaluate the safety and efficacy of Ultomiris administered by intravenous infusion to adult patients with PNH who are naïve to complement inhibitor treatment.

Additionally, this study aims to collect and evaluate safety data specific to the use of Ultomiris and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in treated PNH patients.

– List of addressed safety concerns:
  Meningococcal infection
  Serious haemolysis after drug discontinuation in PNH patients
  Immunogenicity
  Serious infections
  Malignancies and haematologic abnormalities in PNH patients
  Use in pregnant and breast-feeding women

ALXN1210-PNH-302

Purpose of the study: This Phase 3 study aims to assess the noninferiority of Ultomiris in adult patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months.

Additionally, this study aims to collect and evaluate safety data specific to the use of Ultomiris and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in treated PNH patients.

– List of addressed safety concerns:
  Meningococcal infection
  Serious haemolysis after drug discontinuation in PNH patients

Serious infections
Malignancies and haematologic abnormalities in PNH patients
Use in pregnant and breast-feeding women

M07-001: PNH Registry

Purpose of the study: This registry aims to collect and evaluate safety data specific to the use of Soliris / Ultomiris and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in Soliris / Ultomiris and non-Soliris / Ultomiris treated PNH patients.

– List of addressed safety concerns (Ultomiris):
Meningococcal infection
Serious haemolysis after drug discontinuation in PNH Patients
Serious infections
Malignancies and haematologic abnormalities in PNH patients
Use in pregnant and breast-feeding women

M11-001: aHUS Registry

Purpose of the study: The registry aims to collect and evaluate safety and effectiveness data specific to the use of eculizumab / ravulizumab 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 / ravulizumab treatment or other disease management.

– List of addressed safety concerns (Ultomiris):
Meningococcal infection
Severe TMA complications in aHUS patients after ravulizumab discontinuation
Immunogenicity
Serious infections
Use in pregnant and breast-feeding women

ALXN1210-aHUS-311

Purpose of the study: The objective of the study is to assess the efficacy and long-term safety of ravulizumab in complement inhibitor treatment-naïve adolescent and adult patients with aHUS to inhibit complement-mediated TMA as characterised by thrombocytopenia, haemolysis, and renal impairment.

– List of addressed safety concerns:
Meningococcal infection
Severe TMA complications in aHUS patients after ravulizumab discontinuation
Immunogenicity
Serious infections
Use in pregnant and breast-feeding women