Summary of risk management plan for UPLIZNA (inebilizumab)

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

UPLIZNA's SmPC and its PL give essential information to healthcare professionals and patients on how UPLIZNA should be used.

This summary of the RMP for UPLIZNA 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 UPLIZNA's RMP.

I. The medicine and what it is used for

UPLIZNA is authorised for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD) to reduce the risk of attacks and associated worsening of disability (see SmPC for the full indication). It contains inebilizumab as the active substance and it is given by IV administration.

Further information about the evaluation of UPLIZNA's benefits can be found in UPLIZNA's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: *https://www.ema.europa.eu/en/medicines/human/EPAR/uplizna*.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of UPLIZNA, together with measures to minimise such risks and the proposed studies for learning more about UPLIZNA'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 PL 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 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 UPLIZNA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of UPLIZNA 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 UPLIZNA. 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 II.A.1: List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Infusion reaction. • Neutropenia.
Important potential risks	• Serious infections, viral reactivation, and opportunistic infections. • PML. • Malignancy. • Blood disorders, particularly decrease in B-cell levels in foetal and newborns exposed to inebilizumab in pregnant women.
Missing information	• Safety in patients > 65 years. • Use during pregnancy and lactation. • Patients concomitantly receiving other immunosuppressive agents.

II.B Summary of important risks

Table II.B.1: Summary of important risks

Important identified risk 1: Infusion Reaction	
Evidence for linking the risk to the medicine	The source of information is clinical trial data.
Risk factors and risk groups	There are no identified risk factors for infusion reactions. Infusion reactions were more common during the first infusion that during subsequent infusions.

Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.4, Section 4.8, Section 5.1. PL Section 2 and Section 4. Recommendations for proper administration in SmPC Section 4.2 and Section 4.4. Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** None

Important identified risk 2: Neutropenia	
Evidence for linking the risk to the medicine	The source of information is clinical trial data.
Risk factors and risk groups	There are no known risk factors for neutropenia with inebilizumab treatment.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8. PL Section 4. Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** None

Important potential risk 1: Serious Infections, Viral Reactivation, and Opportunistic Infections	
Evidence for linking the risk to the medicine	The source of information is clinical trial data and medical literature.
Risk factors and risk groups	Known HBV infection is a risk factor for HBV reactivation. Concomitant use of inebilizumab with immunosuppressive agents, including systemic corticosteroids, may increase the risk of infection. Use of inebilizumab in patients known immunodeficiencies may increase the risk of infection. The

	safety of immunisation with live or live-attenuated vaccines following inebilizumab dosing has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during inebilizumab treatment and until B-cell repletion.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.3, Section 4.4, Section 4.5, and Section 4.8. PL Section 2 and Section 4. Recommendations for infection assessment before administration in SmPC Section 4.2. Clinical setting: IV product that can only be administered in an infusion centre or hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** Patient card

Important potential risk 2: Progressive Multifocal Leukoencephalopathy	
Evidence for linking the risk to the medicine	The source of information is clinical trial data and medical literature.
Risk factors and risk groups	There are no known risk factors for PML in patients treated with B-cell-depleting therapies.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.3 and 4.4. PL Section 2 and Section 4. Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** Patient card

Important potential risk 3: Malignancy	
Evidence for linking the risk to the medicine	The source of information is clinical trial data and medical literature.
Risk factors and risk groups	There are no known risk factors for malignancy in patients treated with inebilizumab.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.3 and 4.4, PL Section 2 Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** None

Important potential risk 4: Blood disorders, particularly decrease in B-cell levels in foetal and newborns exposed to inebilizumab in pregnant women	
Evidence for linking the risk to the medicine	The source of information is non-clinical trial (animal) data.
Risk factors and risk groups	Foetuses and newborns may be at risk of blood disorders as inebilizumab may cross the placenta and deplete B-cells.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.4, 4.6 and 5.3. Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** None

Missing information 1: Safety in patients > 65 years	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 and Section 5.2. Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only.

	Additional risk minimisation measures: None

Missing information 2: Use during pregnancy and lactation	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.6. PL Section 2. Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** None

Missing information 3: Patients concomitantly receiving other immunosuppressive agents	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.5. PL Section 2. Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** None

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 for UPLIZNA.

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

SPHERES Registry Study

CorEvitas SPHERES Registry for NMOSD (Sponsored and managed by CorEvitas).

Purpose of the study:

To prospectively study the natural history of NMOSD and the comparative effectiveness and comparative safety of approved and off-label medications used in the treatment of NMOSD, as well as to systematically evaluate the burden for patients with this disease and to describe treatment utilisation patterns. AEs of special interest (Targeted Events) including the important risks and missing information such as serious infections, malignancies, severe hypersensitivity reactions/anaphylaxis, and pregnancy will be evaluated.

Pregnancy Registry Study

An Observational Pregnancy Safety Study in Women with NMOSD Exposed to UPLIZNA® (inebilizumab-cdon) during Pregnancy.

Purpose of the study:

The registry is conducted to better characterise how inebilizumab commercial product (UPLIZNA) may affect pregnancy and infant outcomes. The specific objectives are:

- To assess pregnancy and birth outcomes in female patients with NMOSD, exposed to inebilizumab commercial product (UPLIZNA) during pregnancy as defined by receipt of any dose during pregnancy or within 6 months preceding conception.
- To describe major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births, if they occur, in women with gestational exposure to UPLIZNA.

Real-World Observational Study

Real-World Observational Study of Outcomes for Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) Treated With inebilizumab in Europe

Purpose of the study:

The study will seek to assess patterns of drug utilization and to quantify outcomes related to safety and effectiveness in new users of inebilizumab. The specific objectives are:

- To describe the characteristics (including demographics, disease burden, selected comorbidities and concomitant medication use) of NMOSD patients who initiate treatment with inebilizumab.
- To assess treatment and drug utilization patterns of NMOSD patients who initiate treatment with inebilizumab, and
- To observe clinical and treatment outcomes by estimating the occurrence of events of interest including infusion related reactions, serious infections including PML, and malignancy.

Post-authorization Safety Study

A safety study of NMOSD for patients receiving inebilizumab following closure of the open-label period N-MOMENTUM Study

Purpose of the study:

To understand the long-term effects of inebilizumab by collecting safety, laboratory, and other data from patients receiving long-term treatment with inebilizumab, and following discontinuation of inebilizumab. To assess specific safety, laboratory, and other measures in patients with NMOSD, during long-term treatment with inebilizumab and following its discontinuation.