PIAKSY®
Injektionslösung/Infusionslösung
340 mg/2 ml (170 mg/ml)
Zul.-Nr. 69’340

Public Risk Management Plan (RMP) Summary

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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 “Piasky” 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 “Piasky” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. “Roche Pharma (Schweiz) AG” is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Piasky”.

PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

Summary of Risk Management Plan for Piasky (Crovalimab)

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

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

This summary of the RMP for crovalimab 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 Crovalimab's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Crovalimab as monotherapy is indicated for the treatment of adult and pediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (see SmPC for the full indication).

- In patients with haemolysis with clinical symptom(s) indicative of high disease activity.
- In patients who are clinically stable after having been treated with a complement component 5 inhibitor for at least the past 6 months

It contains crovalimab as the active substance, and it is given by IV infusion and SC injection.

Further information about the evaluation of the benefits of crovalimab can be found in the EPAR for crovalimab, including the plain-language summary, available on the EMA Web site, under the medicine's Web page

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

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

Measures to minimize 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 authorized pack size—The amount of medicine in a pack is chosen so as 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 minimize its risks.

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

In the case of crovalimab, these measures are supplemented with *additional risk-minimization* measures mentioned under relevant risks below.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, 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 crovalimab is not yet available, it is listed under "missing Information" below.

II.A List of Important Risks and Missing Information

Important risks of crovalimab are risks that need special risk-management activities to further investigate or minimize 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 crovalimab. 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 about 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	• Serious infections • Infusion and injection-related reactions • Type III immune complex reactions (patients switching from eculizumab or ravulizumab to crovalimab (and vice versa)) • Meningococcal infection • Immunogenicity
Important potential risks	• Serious hemolysis after drug discontinuation • Malignancies and hematological abnormalities
Missing information	• Use in pregnancy and/or breastfeeding

II.B Summary of Important Risks

Important Identified Risk: Serious Infections	
Evidence for linking the risk to the medicine	Serious infections that are not meningococcal infections are a class effect. This important identified risk for crovalimab is based on data from the crovalimab safety-evaluable population in the Phase III studies (BO42162, YO42311, and BO42161) and the supportive Phase I/II Study BP39144.
Risk factors and risk groups	Treatment with crovalimab may increase susceptibility to serious infections since it blocks terminal complement activation. In addition, PNH patients with leukopenia may have an increased risk of serious infections.
Risk-minimization measures	**Routine risk minimization measures:** Routine risk communication is described in: • SmPC Section 4.4 – Special warnings and precautions for use Recommendation to vaccinate patient per local guidelines to prevent *Streptococcus pneumoniae* and *Haemophilus influenzae* type b infections. Recommendation to monitor patients closely with an active systemic infection for signs and symptoms of worsening infection. **Additional risk minimization measures:** Education materials: guides for prescribing HCPs and patients/caregivers.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study MO45473 See Section II.C of this summary for an overview of the post-authorization development plan

HCP = healthcare professional; PNH = paroxysmal nocturnal hemoglobinuria; SmPC = Summary of Product Characteristics.

Important Identified Risk: Infusion- and Injection-Related Reactions	
Evidence for linking the risk to the medicine	IRRs and systemic injection-related reactions are a class effect for other complement C3 and C5 inhibitor therapies. In clinical trials of PNH patients with eculizumab, no patients experienced an IRR that required discontinuation of treatment. In clinical trials with ravulizumab (across several indications), IRRs occurred in approximately 1% of patients who were treated with ravulizumab. These events included lower back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, allergic reaction, dysgeusia, and drowsiness. None of the events led to treatment discontinuation. In clinical trials with pegcetacoplan, systemic hypersensitivity reactions have occurred in patients treated with pegcetacoplan, with 1 patient experiencing a serious allergic reaction which resolved after treatment. This important identified risk was established based on data from the crovalimab safety-evaluable population in the Phase III studies (BO42162, YO42311, and BO42161) and the supportive Phase I/II Study BP39144.
Risk factors and risk groups	Patients with previous history of anaphylaxis and atopic individuals are risk groups. Since anaphylaxis can be immunologically-mediated, ADAs may be a risk factor, as they could lead to the formation of circulating immune complexes resulting in generalized hypersensitivity reactions. Otherwise, there are no reliable predictors of patients who may or may not be susceptible to systemic infusion- and injection-related reactions due to crovalimab administration.
Risk-minimization measures	**Routine risk-minimization measures:** Routine risk communication is described in: • SmPC Section 4.2 – Posology and method of administration Recommendation that patient/caregiver may administer SC dosing without HCP supervision after appropriate training, if determined by the treating physician to be appropriate. Recommendation to slow down or interrupt IV loading dose infusion in case of an IRR or discontinue immediately if the patient experiences a serious hypersensitivity reaction. • SmPC Section 4.4 – Special warnings and precautions for use Recommendation for patient/ caregiver to seek immediate medical attention if the patient develops symptoms of serious allergic reactions, including to confirm with the HCP regarding crovalimab treatment continuation, and administration of appropriate therapy. **Additional risk minimization measures:** Education materials: guides for patients/caregivers. Additionally, patient cards will be provided.

Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

ADA = anti-drug antibody; C3 = complement 3; C5 = complement 5; HCP = healthcare professional; IRR = infusion-related reaction; IV = intravenous; PNH = paroxysmal nocturnal hemoglobinuria; SC = subcutaneous; SmPC = Summary of Product Characteristics

Important Identified Risk: Type III immune complex reactions (in patients switching from eculizumab or ravulizumab to crovalimab (and vice versa))	
Evidence for linking the risk to the medicine	This important identified risk was established based on data from the patients who switched C5 inhibitor therapy in the safety-evaluable population in Studies BO42162, BO42161, and BP39144. YO42311 did not contribute to the risk characterization since only treatment-naive patients were enrolled and transient immune complexes only occur in patients switching to/from other C5 inhibitors, which bind different epitopes than crovalimab, and therefore were not relevant or expected in this study.
Risk factors and risk groups	Type III immune complex reactions in patients who switch between complement C5 inhibitor therapies is an emerging risk and thus data on risk factors and risk groups are not yet available.
Risk-minimization measures	**Routine risk-minimization measures:** Routine risk communication is described in: • SmPC Section 4.4 – Special warnings and precautions for use Recommendation to monitor for the first 30 days after switching from eculizumab or ravulizumab to crovalimab for occurrence of the symptoms of Type III immune complex reactions. Guidance provided for appropriate treatments in the event of mild/moderate or severe reactions. **Additional risk minimization measures:** None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

C5 = complement 5; HCP = healthcare professional; SmPC = Summary of Product Characteristics.

Important Identified Risk: Meningococcal Infection	
Evidence for linking the risk to the medicine	Meningococcal infections are a class effect. Life–threatening and fatal meningococcal infections have occurred in patients treated with eculizumab, which is also an anti-C5 mAb. It is associated with an approximate 1000– to 2000–fold increased risk of meningococcal disease in comparison to the general U.S. population annual rate (0.11–0.12 per 100,000 in 2015–2017). Meningococcal infection may become rapidly life–threatening or fatal if not recognized and treated early. In clinical studies in PNH patients with eculizumab, 2 out of 196 PNH patients developed serious meningococcal infections; both had been vaccinated. In ravulizumab clinical studies in PNH patients, 3 out of 261 adult PNH patients developed serious meningococcal infections/sepsis; all 3 patients had been vaccinated. No meningococcal infections occurred among pediatric patients (n = 13) receiving ravulizumab in clinical trials. In clinical studies of pegcetacoplan in PNH patients, there were no reports of meningococcal infections. There were no events of meningococcal infection in patients with PNH receiving crovalimab in the Phase III studies (BO42162, YO42311, and BO42161) and the supportive Phase I/II Study BP39144. However, there was 1 patient with a Grade 3 meningococcal infection (*Neisseria meningitidis* serotype X) that resolved in Study BO42354, a study evaluating crovalimab in pediatric patients with aHUS; the patient was vaccinated according to protocol requirements. This important identified risk was established based on the fact that it is considered a class effect due to the mechanism of action and data from the aHUS study where 1 patient treated with crovalimab had a meningococcal infection.
Risk factors and risk groups	Antecedent viral infection, household crowding, and smoking are the main risk factors for meningococcal disease in the general population. The following risk groups relevant in PNH are at increased risk for meningococcal disease: persons with persistent complement component deficiency and persons who use complement inhibitors (including crovalimab).

Important Identified Risk: Meningococcal Infection (cont.)	
Risk-minimization measures	**Routine risk-minimization measures:** Routine risk communication is described in: • SmPC Section 4.3 – Contraindications • SmPC Section 4.4 – Special warnings and precautions for use Requirement to vaccinate patient with a tetravalent meningococcal vaccine at least 2 weeks prior to receiving the first dose of crovalimab treatment; or if immediate therapy with crovalimab is indicated in an unvaccinated patient, the required vaccination should be administered as soon as possible and patients should receive prophylactic antibiotics from the time they start crovalimab treatment until 2 weeks after vaccination; and to maintain up to date vaccinations according to current local guidelines. Recommendation to closely monitor patient for worsening of PNH symptoms (including hemolysis) upon vaccination. Recommendation to monitor patient for early signs of meningococcal infection and consider use of antibiotics based on local guidance, to inform patient of these signs and symptoms and steps and urge them to seek medical care immediately. Physician must discuss the benefits and risks of crovalimab treatment with patients. Recommendation to provide patient with a patient card and patient guide. **Additional risk minimization measures:** • Education materials: guides for prescribing HCPs and patients/caregivers • Patient card • Controlled access program • Vaccination/re-vaccination reminder
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study MO45473 See Section II.C of this summary for an overview of the post-authorization development plan

aHUS = atypical hemolytic uremic syndrome; C5 = complement 5; HCP = healthcare professional; mAb = monoclonal antibody; PNH = paroxysmal nocturnal hemoglubinuria; SmPC = Summary of Product Characteristics

Important Identified Risk: Immunogenicity	
Evidence for linking the risk to the medicine	This risk is based on the known theoretical risk for all therapeutic proteins, including mAbs. ADAs to eculizumab and to ravulizumab have been detected in the Phase III PNH program; however, no apparent correlation of ADA development to clinical response was observed for either molecule. Evidence for loss of exposure and efficacy with crovalimab in PNH is based on PK, PD activity (CH50 or free C5) and clinical response (LDH) from crovalimab Phase III studies (BO42162, YO42311, and BO42161).
Risk factors and risk groups	There is no single risk factor for the development of ADAs. Both patient and product specific factors can affect immunogenicity, e.g., prior sensitization/history of allergy, route of administration and genetic status etc. Patients are specifically at risk of reduced efficacy if high titers of high-affinity neutralizing ADAs are present and persistent.
Risk-minimization measures	**Routine risk-minimization measures:** Routine risk communication is described in: • SmPC Section 4.4 – Special warnings and precautions for use Requirement to monitor for clinical signs of loss of exposure and efficacy, including serious intravascular hemolysis. In the event of persistent serious intravascular haemolysis despite compliant treatment with crovalimab, patients should be promptly assessed to evaluate the aetiology and the possibility of the development of ADAs leading to loss of exposure and efficacy should be considered. An assessment of the benefits versus risks of continuing crovalimab should be made and a switch to an alternative therapy should be considered. Patients/caregivers should be advised to seek immediate attention if the patient develop signs of worsening PNH. • SmPC Section 4.8– Undesirable Effects Recommendation that patient is promptly evaluated by a HCP in case of clinical signs of loss of efficacy following guidance provided in SmPC Section 4.4. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

ADA = anti-drug antibody; HCP = healthcare professional; mAb = monoclonal antibody; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglubinuria; SC = subcutaneous; SmPC = Summary of Product Characteristics

Important Potential Risk: Serious Hemolysis after Drug Discontinuation	
Evidence for linking the risk to the medicine	Serious hemolysis following treatment discontinuation from a complement-targeted therapy is a class effect due to the mechanism of action of complement C3 and C5 inhibitors. Patients with PNH treated with eculizumab/ravulizumab/pegcetacoplan are informed that they may develop hemolysis due to PNH following discontinuation and that they should be monitored by their HCP following treatment discontinuation. This important potential risk is a theoretical possibility in patients with PNH treated with crovalimab, based on the mode of action of crovalimab and the nature of PNH.
Risk factors and risk groups	No clear risk factors or risk groups have been identified due to the low number of patients who discontinued crovalimab treatment.
Risk-minimization measures	**Routine risk-minimization measures:** Routine risk communication is described in: • SmPC Section 4.4 – Special warnings and precautions for use Requirement to closely monitor patient for signs and symptoms of serious intravascular hemolysis upon treatment discontinuation if patient does not switch to another treatment for PNH. **Additional risk minimization measures:** Education materials: guides for prescribing HCPs and patients/caregivers.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study MO45473 See Section II.C of this summary for an overview of the post-authorization development plan.

C3 = complement 3; C5 = complement 5; HCP = healthcare professional; PNH = paroxysmal nocturnal hemoglubinuria; SmPC = Summary of Product Characteristics

Important Potential Risk: Malignancies and Hematological Abnormalities	
Evidence for linking the risk to the medicine	Crovalimab is a complement C5 inhibitor mAb that blocks terminal complement activation; therefore, patients may be at risk of developing malignancies or hematological abnormalities.
Risk factors and risk groups	No clear risk factors or risk groups have been identified due to the low number of patients who had a malignancy or hematological abnormality following crovalimab treatment.
Risk-minimization measures	**Routine risk-minimization measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study MO45473 See Section II.C of this summary for an overview of the post-authorization development plan

C5 = complement 5; mAb = monoclonal antibody

Missing Information: Use in Pregnancy and/or Breastfeeding	
Risk-minimization measures	**Routine risk-minimization measures:** Routine risk communication is described in: • SmPC Section 4.6 – Fertility, pregnancy and lactation Recommendation for a female of child-bearing potential who is prescribed crovalimab to contact her physician if the patient intends to become or suspects that she is pregnant. Recommendation that the HCP consider whether to discontinue breast-feeding or to discontinue from crovalimab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study MO45473 See Section II.C of this summary for an overview of the post-authorization development plan.

HCP = healthcare professional; SmPC = Summary of Product Characteristics.

II.C Post-Authorization Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorization

There are no studies that are conditions of the marketing authorization or specific obligation of crovalimab.

II.C.2 Other Studies in Post-Authorization Development Plan

Study/activity short name and title: Crovalimab Safety Study to Characterize Safety Events and Special Conditions Including Pregnancy and Infant Outcomes in the IPIG Registry (MO45473)
Rationale and Study Objectives: In order to gather more information on the safety of crovalimab in the real world, Roche has entered a partnership with the IPIG Registry to co-create a product-specific silo in the IPIG registry and collect additional serious adverse events and events of special interest such as serious infections, serious hemolysis after drug discontinuation, malignancies and hematologic abnormalities, as well as pregnancy and infant outcomes in patients treated with crovalimab. This will aid in monitoring the overall safety of crovalimab after its country-specific approval. The primary objectives for this study are as follows: • To estimate the frequency of adverse events among patients exposed to crovalimab (i.e. cases of serious hemolysis in patients who discontinue crovalimab, serious infections, meningococcal infection, and malignancies and hematologic abnormalities) • To evaluate pregnancy and infant outcomes in crovalimab-exposed PNH patients To estimate the frequency of adverse pregnancy outcomes (during pregnancy and during 1 year postpartum) and birth outcomes (i.e., live births, spontaneous abortions, stillbirths, elective terminations, and preterm births) To estimate the frequency of adverse fetal/neonatal/infant outcomes (i.e., major and minor congenital malformations, gestational age, postnatal growth and development) and serious safety events at birth and through at least the first year of life of infants Estimate the frequency of serious safety event and infant outcomes among women treated with crovalimab by breastfeeding status
Study Design This is a multi-center, multi-national, observational, non-interventional, secondary data use study that will describe post-authorization safety and effectiveness data among PNH patients exposed to crovalimab, including pregnant women. The primary data collection will be conducted in Study MO44987, referred to as the “Crovalimab Silo”. The Crovalimab Silo is a product-specific silo registry part of the IPIG PNH disease registry (referred to as the “Core registry”). Approximately 300 patients are expected to be enrolled in the crovalimab silo. Patients will be followed up during their crovalimab treatment and up to 12 months after discontinuation (or up to 12 weeks if they start treatment with a new complement inhibitor).
Milestones: Final Protocol: 31 December 2024 First Interim Report: 31 October 2026 (subsequent reports to be provided every 2 years thereafter with the PBRER) Final Clinical Study Report: 31 December 2036

IPIG = International PNH Interest Group; PBRER = Periodic Benefit-Risk Evaluation Report; PNH = paroxysmal nocturnal hemoglobinuria.