swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Piasky

International non-proprietary name:	crovalimab
Pharmaceutical form:	solution for injection/infusion
Dosage strength(s):	340 mg/2 mL
Route(s) of administration:	intravenous, subcutaneous
Marketing authorisation holder:	Roche Pharma (Schweiz) AG
Marketing authorisation no.:	69340
Decision and decision date:	approved on 13 February 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
C5	Component 5
CH50	Complement activity
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
$C_{trough,ss}$	Trough plasma concentration at steady-state
cyFcRn	Cynomolgus monkey neonatal Fc receptor
CYP	Cytochrome P450
DDI	Drug-drug interaction
DTDC	Drug-target-drug complex
EMA	European Medicines Agency
ePPND	Enhanced pre- and postnatal development
ERA	Environmental risk assessment
FACIT	Functional Assessment of Chronic Illness Therapy
FcRn	Neonatal fragment crystallisable receptor
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
hFcRn	Human neonatal Fc receptor
Hgb	Haemoglobin
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
IE HPLC	Ion-exchange high-performance liquid chromatography
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
IV	Intravenous
Ka	Absorption rate constant
K_D	Equilibrium dissociation constants
LDH	Lactate dehydrogenase
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
NR-SE-HPLC	Non-reducing size exclusion high-performance liquid chromatography
NR-CE-SDS	Non-reducing capillary electrophoresis sodium dodecyl sulfate
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics

Ph. Eur.	Pharmacopoea Europaea
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal haemoglobinuria.
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
QTc	Corrected QT interval
QTcB	QTc corrected by Bazett's formula
QTcF	QTc corrected by Fridericia's formula
QW	Once a week
Q4W	Every 4 weeks
RBC	Red blood cell
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous
SwissPAR	Swiss Public Assessment Report
$t_{1/2}$	Terminal half-life
TA	Transfusion avoidance
TEAE	Treatment-emergent adverse event
Tmax ss	Median time to maximum concentration at steady state
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
ULN	Upper limit of normal
USP	US Pharmacopeia
WBC	White blood cell

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for crovalimab in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 28 March 2023.

2.2 Indication and dosage

2.2.1 Requested indication

Piasky is indicated for the treatment of adult and paediatric patients with paroxysmal nocturnal haemoglobinuria.

2.2.2 Approved indication

Piasky as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH):

- 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

See sections «*Warnings and precautions*» *and* «*Properties/effects, Clinical efficacy*».

2.2.3 Requested dosage

Dosing regimen based on body weight

Body Weight	≥40 kg to <100 kg	≥100kg
Loading Dose		
Day 1	1000 mg (IV)	1500 mg (IV)
Day 2, 8, 15, 22	340 mg (SC)	340 mg (SC)
Maintenance Dose		
Day 29 and Q4W thereafter	680 mg (SC)	1020 mg (SC)

IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	5 September 2023
Formal control completed	2 October 2023
List of Questions (LoQ)	30 January 2024
Response to LoQ	29 April 2024
Preliminary decision	19 July 2024
Response to preliminary decision	16 September 2024
Labelling corrections and/or other aspects	27 November 2024
Response to labelling corrections and/or other aspects	20 December 2024
Final decision	13 February 2025
Decision	approval

3 Medical context

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare haematological disease with an incidence of 1-1.5 cases per million (international data, no exact data for Switzerland available). Clinical presentation varies considerably. Symptoms include haemolytic anaemia, thrombosis, renal impairment, and fatigue. PNH is a serious and potentially life-threatening disease. Historical retrospective data from a UK cohort demonstrate a reduced life expectancy of PNH patients.[1] The central role of the complement system in PNH has led to the successful use of complement inhibitors in the treatment of PNH.[2]

4 Quality aspects

4.1 Drug substance

Fehler! Verweisquelle konnte nicht gefunden werden. is a humanised monoclonal antibody (IgG1,κ) that binds to C5 complement protein, inhibiting C5 cleavage into C5a and C5b, thus preventing the formation of the membrane attack complex, averting membrane disruption, and consequently eliminating cell lysis. **Fehler! Verweisquelle konnte nicht gefunden werden.** consists of two heavy and two light chains connected by inter-chain disulfide bonds. Both heavy chains contain one oligosaccharide chain in the conserved Fc site (Asn303).
Fehler! Verweisquelle konnte nicht gefunden werden. is expressed in a Chinese hamster ovary (CHO) cell line, and is manufactured using a fed-batch production process in a production bioreactor. The cell culture fluid is harvested, and the antibody is purified by several chromatographic and filtration steps, including virus inactivation and virus removal steps. The drug substance manufacturing process is performed by Roche Diagnostics GmbH, Penzberg, Germany. The fermentation and purification process was validated using four consecutive batches, demonstrating a consistent manufacturing process that effectively reduces process-related impurities. The physicochemical and biological properties of the drug substance and its impurities were characterised using state-of-the-art methods.
The specifications for release include relevant tests and limits, e.g. for description, colour, clarity, identity, several purity/impurity tests (e.g. NR-SE-HPLC, NR-CE-SDS, IE-HPLC), protein concentration, and potency assay (liposome immunoassay). Specifications are based on clinical data and batch analysis and are in conformance with current compendial or regulatory guidelines. Batch analysis data of development, clinical and process validation batches were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release. All specific analytical methods are described and are fully validated.
The drug substance is stored frozen. No changes were observed within the proposed storage conditions. A shelf-life of 36 months with long-term storage at -40±10°C has been accepted.

4.2 Drug product

The finished product **Fehler! Verweisquelle konnte nicht gefunden werden.** is available as a 340 mg product supplied as sterile solution with no preservatives in a single-use vial. It is intended for intravenous infusion together with normal saline or subcutaneous injection. All excipients used comply with the European Pharmacopoeia (Ph. Eur.).
The finished product manufacturing process consists of sterile filtration, aseptic filling, capping and inspection steps and is conducted at Genentech, South San Francisco, California, USA, or Roche

[1] Hillmen P. et al., N Engl J Med 1995; 333:1253-1258
[2] Risitano AM et al. Front. Immunol. 2019, 10:1664-3224

Diagnostics GmbH, Mannheim, Germany. Process validation studies were executed at commercial scale using three validation batches.
The release and stability specifications include relevant tests and limits, e.g. for appearance, identity, pH, osmolality, purity and impurity (SE-HPLC, NR-CE-SDS, IE-HPLC), protein concentration, potency assay (liposome immunoassay), particles, sterility, and bacterial endotoxins. All specific methods are validated in accordance with ICH guidelines. Batch analysis data from development, clinical and process validation batches were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release.
The drug product is stored in 2 mL Type I clear glass vials at 2 - 8°C, protected from light. Each vial is closed with a butyl rubber stopper. The stoppered vial is sealed with an aluminium closure with a flip-off button. All components are Ph. Eur. and US Pharmacopeia (USP) compliant. A shelf-life of 36 months has been accepted.

4.3 Quality conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf-life of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk of adventitious agents is minimised.

5 Nonclinical aspects

The nonclinical development programme for Piasky with the new active substance crovalimab, a humanised anti-complement component 5 (C5) IgG1 monoclonal antibody, followed relevant ICH guidelines, in particular ICH S6(R1). The pivotal nonclinical safety studies were performed in compliance with GLP.

5.1 Pharmacology

Crovalimab bound to human C5 (hC5) and cynomolgus monkey C5 (cyC5) with equilibrium dissociation constants (K_D) of 1.72×10^{-10} M and 2.00×10^{-10} M. Crovalimab did not bind to rat C5 and bound approx. 85-fold weaker to mouse C5 than to human C5. Crovalimab dose-dependently inhibited lysis of chicken red blood cells (RBCs) in human and cynomolgus monkey serum with IC_{50} values in the subnanomolar range, but not in rat or rabbit serum. The cynomolgus monkey was selected for toxicological studies because of the notable cross-reactivity of C5 to crovalimab.
In cynomolgus monkeys, repeated intravenous (IV) or subcutaneous (SC) administration of crovalimab resulted in a dose-dependent inhibition of 50% haemolytic complement activity (CH50) and marked reduction of RBC haemolysis. Free C5 concentration correlated inversely with crovalimab dosing. The activity of crovalimab was considered independent of FcγRs because of its low affinity towards these receptors. In conclusion, crovalimab inhibited concentration-dependently and reversibly C5 cleavage and terminal complement activity through binding to C5.
The affinity of crovalimab to hFcRn and cyFcRn at pH 6 was approximately 10-fold stronger than the affinity of control IgGs, which is consistent with the long plasma half-life of crovalimab *in vivo* through enhancing the FcRn-mediated recycling following endocytotic uptake.
In line with ICH S6(R1), safety pharmacology endpoints were incorporated into the repeat-dose toxicology studies in cynomolgus monkeys. No adverse effects on the cardiovascular, central nervous or respiratory systems were seen.

5.2 Pharmacokinetics

The pharmacokinetics of crovalimab in cynomolgus monkeys following repeated SC and IV administration revealed a dose-exposure proportionality, a long half-life ($t_{1/2}$) up to 77 days, and a volume of distribution similar to other IgG antibodies, suggesting that crovalimab mainly distributes within circulating blood. Bioavailability was 69.1% following SC administration. There were no sex-related differences in exposure. The pharmacokinetic parameters were comparable with those in humans. ADAs were detected in several animals without any noteworthy impact on drug exposure in the repeat-dose studies. Crovalimab was shown in the enhanced pre- and postnatal development study (ePPND) to pass through the placental barrier. Terminal $t_{1/2}$ in plasma of infants was comparable to that of maternal animals.
No dedicated studies were submitted regarding distribution, metabolism, excretion or drug interactions, which is in line with ICH S6(R1). Transfer to milk was not studied but is expected as IgG antibodies are usually secreted into milk.

5.3 Toxicology

In cynomolgus monkeys, crovalimab was administered SC (weekly, up to 100 mg/kg) and IV (every other week, up to 160 mg/kg) for up to 26 weeks. Crovalimab was well tolerated and there were no adverse crovalimab-related findings. Apart from the pharmacological effect, only slight inflammatory changes at the SC injection sites were observed. In some animals, ADA was associated with a mild non-adverse sporadic arteritis observed in several organs, in addition to glomerulonephritis that was

observed in one animal. No clinical signs were observed. The relevance of these findings for humans in considered to be low.
As crovalimab blocks terminal complement activation, treated human subjects may have increased susceptibility to infections. This is adequately mentioned in the Information for healthcare professionals and as an important identified risk in the RMP.

No genotoxicity studies with crovalimab were submitted, which is in line with ICH S6(R1).

According to ICH S6(R1), carcinogenicity studies are not warranted and were not conducted. Since crovalimab only binds weakly to rodent C5, rodent species are not considered relevant for the assessment of the carcinogenic risk. No evidence of neoplastic or preneoplastic lesions was observed in any organs or tissues in monkeys following chronic administration of crovalimab. Based on the applicant's carcinogenicity assessment, which also included a review of published literature, there is no increased tumour risk by C5-specific antagonism. Therefore, the carcinogenicity potential is considered low. However, malignancies are potential risks of other C5 inhibitors such as eculizumab and ravulizumab, due to their inhibitory effect on the immune system. This is adequately mentioned in the Information for healthcare professionals and as an important identified risk in the RMP.
In the ePPND study, crovalimab was well tolerated by maternal monkeys. No adverse effects of crovalimab on pregnancy or on the viability, growth or development of the infants or juvenile monkeys were identified up to 6 months postpartum. A 50% transient reduction in CH50 was noted in the infants of dams given 100 mg/kg QW.

Systemic exposures based on C_{max} and AUC at the NOAELs in the toxicity studies with crovalimab were 16 to 18-fold higher than the predicted human therapeutic exposures in patients with PNH.

Crovalimab was immunogenic as shown in the repeat-dose studies, showing a tissue cross-reactivity as anticipated for secreted C5 protein and a low cytokine release potential. Its haemolytic potential was low *in vitro*. There are no safety concerns regarding excipients or drug substance- or drug product-related impurities.

The RMP adequately addresses the nonclinical findings and their relevance for clinical use.
There is no risk for the environment due to the protein nature of crovalimab.

5.4 Nonclinical conclusions

The pharmaco-toxicological profile of crovalimab is sufficiently characterised. The submitted nonclinical data support the approval of crovalimab in the proposed indication. The relevant nonclinical safety information is included in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

ADME
PK data from four clinical studies were included in this submission, i.e. COMPOSER, COMMODORE-1, COMMODORE-2 and COMMODORE-3. PK characteristics were described within each study and across the four studies using a popPK approach.

A total of 6115 crovalimab concentrations measured in 9 healthy volunteers and 421 patients with PNH from these four studies were included in the popPK model. Of the 421 PNH patients, 210 were treatment-naïve PNH patients and 211 were switch PNH patients. The PK profiles were best described using a two-compartment open model with first-order elimination and a first-order absorption to describe SC administration.

Absorption
The absorption rate constant (Ka) was estimated to be 0.126 day^{-1} (90% confidence interval [CI]: 0.105−0.176 day^{-1}). Across the Phase III studies, the median time to maximum concentration at steady state ($T_{max,ss}$) occurred at 8.3 days (range: 5.29−11.5 days) following the SC administration. The absolute bioavailability following SC administration was estimated to be 83% compared to the IV administration, based on the results of the popPK analysis.

Distribution
The central volume and peripheral volume of distribution (V2 and V3) were 3.23 L (90% CI: 3.16−3.29 L) and 2.32 L (90% CI: 2.02−2.67 L), respectively. The inter-compartmental clearance (Q) was 0.168 L/d (90% CI: 0.138−0.221 L/d). The small volume of distribution indicates that crovalimab is likely to be distributed mainly in plasma.

Metabolism
The metabolism of crovalimab was not investigated. Monoclonal antibodies are mainly catabolised by lysosomal proteolysis, followed by the elimination of amino acid.

Elimination
The Cl was estimated to be 0.0791 L/day (90% CI: 0.0678−0.0872 L/day). The $T_{1/2}$ was estimated to be 53.1 days (90% CI: 47.7−58.6 days).

Dose proportionality
Across the investigated dose range, dose proportionality of the PK for crovalimab was observed.

Special populations / intrinsic factors
The impact of special populations and intrinsic factors (i.e. demographics) was investigated via popPK analysis approaches.

There was no impact of race or gender on the PK of crovalimab.

The PK of crovalimab is similar in healthy volunteers vs PNH patients.

The PK of crovalimab is similar in treatment-naïve patients vs PNH patients.

There were no dedicated studies in patients with hepatic or renal impairment because, in general, these factors are not expected to impact the exposure to monoclonal antibodies. The popPK analysis included 46 patients with mild and 1 patient with severe hepatic impairment and 62, 38, and 4 patients with mild, moderate, and severe renal impairment, respectively.

No statistically significant influence of hepatic and renal impairment was found on crovalimab clearance. No dose adjustment is therefore indicated for patients with mild hepatic impairment or with mild, moderate, or severe renal impairment. However, the impact of moderate or severe hepatic impairment on crovalimab exposure is unknown due to the lack of data.

Age was found to have a statistically significant impact on the absorption rate, which was however not clinically relevant.

Clearance and volume parameters were impacted by body weight. The typical V2 and Cl were 3.23 l and 0.0791 l/day in a patient weighing 75 kg, respectively. In comparison, the typical parameters were 2.10 l and 0.0493 l/day in a patient weighing 40 kg and 4.71 l and 0.119 l/day in a patient weighing 130 kg. Based on these results a weight-tiered (with a 100-kg cut-off) flat dosing approach was adopted.

In total, 8.1% of the subjects developed medium/high titres (≥104) of ADA, which was associated with a 24.7% increase in Cl. Exposure in subjects with low ADA titres was similar to that of ADA-negative subjects. No dose adjustment is proposed for ADA-positive subjects.

Interactions
No dedicated drug-drug interaction studies were performed since monoclonal antibodies have a very low interaction potential. The metabolism of monoclonal antibodies does not involve CYP-based metabolism, and monoclonal antibodies do not interact with metabolising enzymes or transporters.

Secondary pharmacology (safety)
Due to the size of monoclonal antibodies, the potential is very low for a prolongation of the QT/QTc interval. Therefore, no dedicated QT/QTc study was performed. Instead, a crovalimab-QT analysis was conducted using observed concentrations and 12-lead ECG data from study BP39144 and the Phase III Studies BO42162, YO42311, and BO42161 in treatment-naïve and switch patients with PNH. No increases in ΔQT_cF or ΔQT_cB with crovalimab concentrations were observed. As expected for monoclonal antibodies, these analyses confirm that there is no potential for QT/QTc interval prolongations following the administration of crovalimab.

Exposure efficacy/safety relationship
Exposure-response analyses indicate that no further reduction in LDH is to be expected for $C_{trough,ss}$ ≥ 100 µg/ml. No relevant difference was observed between treatment-naïve and switch patients, between previous treatments for switch patients, between age or weight categories, or between Asian and non-Asian patients.

No relevant exposure-response relationships were observed regarding safety (such as SAEs, AESI, AEs grade 3 or higher).

6.2 Clinical aspects

The efficacy and safety of crovalimab in patients with PNH was evaluated in the pivotal phase 3 study COMMODORE 2 and supported by results of two additional phase 3 studies (COMMODORE 3 and COMMODORE 1) and one phase 1/2 study COMPOSER.

In the controlled study **COMMODORE-2** crovalimab was compared to eculizumab (non-inferiority) in patients with PNH aged ≥18 years and ≥40 kg who were not previously treated with a complement inhibitor therapy.

The study also included a separate non-randomised descriptive arm (Arm C) enrolling paediatric patients aged <18 years with a body weight of ≥40 kg.

The primary (randomised) treatment period was 24 weeks. In the extension period, patients could continue to receive crovalimab for a maximum of 5 years.

Main inclusion criteria were documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation of WBCs with granulocyte or monocyte clone size of ≥10%, within 6 months prior to randomisation; LDH level ≥2 x ULN at screening; and presence of one or more PNH-related signs or symptoms within 3 months prior to screening. For details regarding the included patient population please refer to the attached Information for healthcare professionals.

The primary efficacy objective of the study was to evaluate the efficacy of crovalimab compared to eculizumab, based on the non-inferiority assessment of the co-primary endpoints transfusion avoidance (TA) 24 weeks on treatment and haemolysis control, measured by LDH $\leq 1.5 \times$ ULN from Week 5 through Week 25 (central laboratory).

Both co-primary efficacy endpoints were met in COMMODORE-2, and non-inferiority in haemolysis control as well as transfusion avoidance of crovalimab compared to eculizumab was demonstrated. In the crovalimab arm, 65.7% (95% CI: 56.9, 73.5) of patients were transfusion-free from baseline through Week 25 compared to 68.1% (95% CI: 55.7, 78.5) of patients in the eculizumab arm. The mean proportion of patients with haemolysis control from Week 5 through Week 25 was 79.3% (95% CI: 72.86, 84.48) for the crovalimab arm and 79.0% (95% CI: 69.66, 85.99) for the eculizumab arm.

Non-inferiority of crovalimab was also demonstrated regarding the key secondary efficacy endpoints (proportion of breakthrough haemolysis, stabilisation of Hgb-levels, and change in FACIT-fatigue score). For details please refer to the attached Information for healthcare professionals.

The main supportive study was the phase III, randomised, controlled trial **COMMODORE-1** in PNH patients on stable treatment with eculizumab who switched to crovalimab. The study comprised 2 randomised arms (Arms A [crovalimab] and B [eculizumab]) with only adult patients (≥18 years old) previously treated with eculizumab and a non-randomised arm (Arm C), with adult and paediatric patients previously treated with eculizumab or ravulizumab. The primary objective of this study was to evaluate the safety, and all efficacy endpoints were descriptive. Descriptive efficacy results presented comparable results for haemolysis control and transfusion avoidance for crovalimab compared to eculizumab. For details, please refer to the attached Information for healthcare professionals.

The data basis for paediatric patients with PNH is limited (n=12, n=9 treatment-naïve). For details regarding efficacy and safety in the paediatric population please refer to the attached Information for healthcare professionals. Further studies evaluating crovalimab in paediatric and adolescent patients with atypical haemolytic uraemic syndrome (aHUS) are ongoing. The applicant was obliged to submit safety results of these studies as a condition.

Crovalimab self-administration or drug administration by a caregiver was permitted starting at Week 9, after training and confirmation of proficiency by the healthcare provider. The majority of subcutaneous injections were administered by healthcare professionals, with an increasing proportion of self-administration up to Week 25 and a further increase after Week 25. If treatment is well-tolerated, and if the physician judges the patient as compliant/competent for self-administration, self-administration was accepted after 9 weeks. For details, please refer to the Information for healthcare professionals.

Treatment with complement inhibitors is associated with relevant toxicity. The most frequent adverse events (AEs ≥ 10%) in patients who were treated with crovalimab were COVID-19, upper respiratory tract infection, pyrexia, neutrophil count decreased, infusion-related reaction and white blood cell count decreased.

The formation of DTDCs and related Type III hypersensitivity reactions are specific to switch patients (patients switching from eculizumab/ravulizumab to crovalimab). Grade 3 Type III immune complex mediated reactions were reported for 19% of switch patients in the pooled population. The most frequent symptoms of Type III hypersensitivity were arthralgia, myalgia, and headache. This relevant risk is adequately reflected in the Information for healthcare professionals.

6.3 Final clinical benefit risk assessment

Efficacy data from COMMODORE-2 in PNH patients who are not previously treated with a complement inhibitor therapy is convincing, with statistically significant results for the co-primary endpoints transfusion avoidance (TA) 24 weeks on treatment and haemolysis control.

Data for crovalimab in patients who switched to crovalimab (COMMODORE 1) are descriptive. However, consistent results are observed in comparison to the results in complement inhibitor-naïve patients.

The safety of crovalimab is manageable, and all relevant risks are adequately described in the Information for healthcare professionals.

The benefit-risk assessment is positive for crovalimab in C5 inhibitor-naïve patients and in patients with ongoing, clinically relevant haemolysis despite C5 inhibitor therapy.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Piasky was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "*Undesirable effects*" section for advice on the reporting of adverse reactions.

Piasky®

Composition

Active substances

Crovalimabum.
Crovalimab is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to complement protein C5 (C5). Crovalimab is produced by using genetic technology "*Chinese Hamster Ovary cells*".

Excipients

Histidinum, acidum asparticum, arginini hydrochloridum, poloxamera 188, aqua ad iniectabile q.s. ad solutionem pro 2 mL.

Pharmaceutical form and active substance quantity per unit

Solution for infusion (IV) / Solution for injections (SC).

Piasky is provided as a sterile clear to strongly opalescent and almost colorless to brownish-yellow solution supplied in a single-use glass vial filled with 2 mL of solution. Each vial contains 340 mg of crovalimab (170 mg/mL).

Indications/Uses

Piasky as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal hemoglobinuria (PNH):

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

See sections "*Warnings and precautions" and "Properties/effects, Clinical efficacy*".

Dosage/Administration

General

Piasky treatment should be initiated under the supervision of a physician experienced in the treatment of hematological disorders.

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Dose recommendation

The recommended dosing regimen consists of one loading dose administered by intravenous infusion (on day 1), followed by four additional weekly loading doses administered by subcutaneous injection (on days 2, 8, 15, and 22). The maintenance dose starts on Day 29 and is then administered every 4 weeks by subcutaneous injection. The doses to be administered are based on the patient's body weight, as shown in Table 1.

For patients switching from treatment with another complement inhibitor, the first intravenous loading dose of Piasky should be administered at the time of the next scheduled complement inhibitor administration. The administration of the additional subcutaneous loading doses and maintenance doses of Piasky will follow as per the schedule shown in Table 1.

Table 1 Piasky Dosing Regimen Based on Body Weight

Body Weight	≥ 40 kg to < 100 kg	≥ 100 kg
Loading Dose		
Day 1	1000 mg (IV)	1500 mg (IV)
Day 2, 8, 15, 22	340 mg (SC)	340 mg (SC)
Maintenance Dose		
Day 29 and Q4W[a] thereafter	680 mg (SC)	1020 mg (SC)

IV = intravenous, SC = subcutaneous

[a] Q4W = every 4 weeks

The dosing schedule is allowed to occasionally vary within 2 days of the scheduled administration day (except at Day 1 and Day 2). The subsequent dose should be administered according to the regular schedule.

Duration of treatment

PNH is a chronic disease and treatment with Piasky is recommended to continue for the patient's lifetime; Piasky is intended for long-term treatment unless the discontinuation of Piasky is clinically indicated *(see section "Warnings and Precautions")*.

Delayed administration or missed doses

If an entire planned dose or part of a planned dose of Piasky is missed, the missing dose or remainder of the planned dose should be administered as soon as possible before the day of the next scheduled dose. The next dose should then be administered on the regular scheduled dosing day. Do not administer two doses or more than the prescribed dose on the same day to make up for a missed dose.

Method of administration

Piasky is administered as an intravenous infusion (first dose) and as a subcutaneous injection (subsequent doses). Comprehensive instructions for Piasky administration are given in section "*Other information, instructions for handling*" and Instructions for use in the patient information.

Intravenous administration

Piasky should be prepared for intravenous administration using suitable aseptic technique. Piasky must be diluted and administered by a healthcare provider (HCP) as an intravenous infusion over 60 minutes ± 10 minutes (1000 mg) or 90 minutes ± 10 minutes (1500 mg). Piasky should not be administered as an IV push or bolus.

Subcutaneous administration

For subcutaneous injection, Piasky must be used undiluted and should be prepared using appropriate aseptic technique. It is recommended to inject Piasky into the abdomen. The injection sites should be rotated with every injection. No data are available yet on injection at other sites of the body. Injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

Administration by the patient and/or caregiver

The patient can self-administer Piasky or the caregiver can administer Piasky without medical supervision from week 9 onwards. The treating physician must deem this to be appropriate and the administration of Piasky should not have caused any relevant toxicity. Training must have been provided beforehand by a healthcare professional.

Monitoring

The initial intravenous administration of Piasky must take place in a controlled setting and be given by a healthcare professional. The subsequent five subcutaneous doses (on days 2, 8, 15, 22 and 29) are to be administered in an environment with monitoring, for example, an infusion centre, clinic or hospital. The patient must be monitored by a healthcare professional during the first 60 minutes following the injection after the first three subcutaneous doses (on days 2, 8 and 15). Monitoring for the subsequent injections can be considered if there have been any infusion/injection adverse reactions. (See section "*Warnings and Precautions*").

Dose Modification

Modification of the maintenance dose is required if the patient's body weight changes to become consistently greater than or lower than 100 kg during the course of therapy (see Table 1 for recommended dosage).

The infusion of Piasky may be slowed or interrupted if the patient develops an infusion related reaction. The infusion should be discontinued immediately if the patient experiences a serious hypersensitivity reaction (see section "*Warnings and Precautions, General*").

Special Dosage Instructions

Hepatic impairment

No dose adjustment is required for patients with mild hepatic impairment. Piasky has not been studied in patients with moderate to severe hepatic impairment *(see sections "Warnings and Precautions, General" and section "Pharmacokinetics").*

Renal impairment

No dose adjustment is required for patients with mild, moderate, or severe renal impairment *(see sections "Warnings and Precautions, General" and section "Pharmacokinetics").*

Elderly patients

No dose adjustment of Piasky is required in patients ≥ 65 years of age *(see section "Pharmacokinetics").*

Children and adolescents

No dose adjustment of Piasky is required in paediatric patients 12 years of age or older with body weight ≥ 40 kg. The safety and efficacy of Piasky in children less than 12 years of age and children with body weight < 40 kg have not yet been established. No data are available.

Contraindications

Piasky is contraindicated in patients:

- with a known hypersensitivity (allergic reaction) to crovalimab or any of the excipients *(*see section *"Warnings and Precautions, General").*
- with unresolved *Neisseria meningitidis* infection.
- not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Piasky treatment outweigh the risks of developing a meningococcal infection. In such cases, prophylactic treatment with appropriate antibiotics should be given from the start of Piasky treatment until 2 weeks after vaccination *(*see section *"Warnings and Precautions, General").*

Warnings and precautions

Meningococcal infection

Due to its mechanism of action, the use of Piasky may increase the patient's susceptibility to meningococcal infections (septicemia and/or meningitis). Cases of serious or fatal meningococcal infections/sepsis have been documented in patients (vaccinated and unvaccinated patients) treated with terminal complement inhibitors, which is a known class effect.

Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. To reduce the risk of infection, all patients must be vaccinated with a tetravalent meningococcal vaccine at least 2 weeks prior to receiving the first dose of Piasky. If immediate therapy with Piasky is indicated in an unvaccinated patient, the required vaccine should be administered as soon as possible and patients should receive prophylactic antibiotics from the time they start Piasky until 2 weeks after vaccination.

Vaccines against serogroups A, C, Y, W, and B where available, are recommended to prevent infections with the commonly pathogenic meningococcal serogroups. Patients must maintain up to date vaccination status according to current local guidelines for vaccination use. If the patient is being switched from other terminal complement inhibitor treatment, physicians should verify that meningococcal vaccination is current according to local guidelines for vaccination use. Vaccination may activate the complement system further. As a result, patients with complement-mediated diseases, including PNH, may experience transient worsening of signs and symptoms of their underlying disease, such as haemolysis. Therefore, patients should be closely monitored for disease symptoms after the recommended vaccination.

Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to the prophylactic use of antibiotics based on local guidance. All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary. Patients should be informed of these signs and symptoms and steps they need to take in seeking medical care immediately. Physicians must discuss the benefits and risks of Piasky therapy with patients and provide them with a patient guide and a patient card.

Serious infections other than meningococcal infection

Due to its mechanism of action, Piasky therapy must be administered with caution to patients with active systemic infections. Patients may have increased susceptibility to infections, especially with *Neisseria* spp. and other encapsulated bacteria. Vaccinations for the prevention of Streptococcus pneumoniae and Haemophilus influenzae type b (Hib) infections should be administered according to local guidelines.

If prescribed by local guidelines, vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) infections must be administered at least 2 weeks before the first administration of crovalimab. In the event that immediate treatment with crovalimab is indicated in an unvaccinated patient, the required vaccination is to be administered as soon as possible and the patient should be given prophylactic antibiotics, namely, from the point onwards when treatment with crovalimab is started until 2 weeks after the vaccination or in accordance with local standard treatment, whichever period is longer.

If Piasky is administered to patients with active systemic infections, then these patients must be closely monitored for signs and symptoms of a worsening of the infection. Patients were excluded from clinical studies conducted with crovalimab if they had suffered an active systemic bacterial, viral or fungal infection within 14 days of starting treatment.

Patients should be given information from the package leaflet to raise their awareness of the signs and symptoms of potentially serious infections.

Type III immune complex reactions

Transient immune complex formation occurs in patients switching between monoclonal antibody complement inhibitors that bind to different epitopes of C5 (*see section "Interactions, Effects of other substances on the pharmacokinetics of crovalimab"*). Switching from another C5 inhibitor to Piasky can result in the formation of these complexes and in Type III immune complex-mediated reactions.

The advantages of switching from another C5 inhibitor to Piasky must therefore be weighed against the risk of Type III hypersensitivity reactions.

Patients who have never previously been treated with a C5 inhibitor or patients in whom previous C5 inhibitor treatment has been cleared from the body (i.e. at least 5.5 half-lives of the previous therapy have passed since last dose) are not at risk of Type III immune complex reactions.

Clinical trials with Piasky reported Type III immune complex reactions *(*see section *"Undesirable effects").*

Signs and symptoms of Type III immune complex reactions observed in clinical trials were arthralgia and other musculoskeletal and connective tissue disorders, rash and other skin and subcutaneous disorders, pyrexia, asthenia/fatigue, gastrointestinal distress, and headache. Type III immune complex reactions may also manifest as renal abnormalities, however this was not observed during clinical trials.

Based on time-to-onset of Type III immune complex reactions observed in clinical trials, it is recommended that patients are monitored for the first 30 days after switching from eculizumab or ravulizumab to Piasky for occurrence of the symptoms of Type III immune complex reactions. For mild or moderate Type III immune complex reactions, administration of symptomatic treatment e.g. topical corticosteroids, antihistamines, antipyretics, and/or analgesics may be considered. For severe reactions, oral or systemic corticosteroid therapy can be initiated and tapered as clinically indicated.

Infusion and injection related reactions

Administration of Piasky may cause infusion-related reactions or systemic injection-related reactions, depending on the route of administration. These may include allergic or hypersensitivity reactions (including anaphylaxis) but also a range of other symptoms like headache or muscle pain.

The first intravenous and first five subcutaneous doses are to be administered in an environment with monitoring (see "*Dosage/Administration*").

Treatment must be interrupted and appropriate medical treatment started in the event of a serious infusion-related reaction after the intravenous administration of Piasky. Patients/caregivers must seek medical advice immediately in cases of a serious injection-related reaction after subcutaneous administration, or any incidence of a severe allergic reaction after intravenous or subcutaneous administration, and appropriate medical treatment must be started. Patients should discuss with their physician whether or not treatment with Piasky can be continued.

Patients must be informed of this risk and the treatment options for severe allergic reactions. In doing so, consideration should also be given to providing patients with an emergency kit (including adrenaline auto-injector) and instructing them in its use. Patients should be instructed to consult a doctor immediately and use the emergency kit in case of severe systemic allergic reactions, angioedema, difficulty swallowing, difficulty breathing, changes in their voice or if they feel as if they have a lump in their throat.

Serious hemolysis after drug discontinuation in PNH patients

In case of Piasky discontinuation, patients who do not switch to another treatment for PNH must be closely monitored for at least 20 weeks for signs and symptoms of serious intravascular hemolysis, identified by elevated lactate dehydrogenase (LDH) levels, along with sudden decrease in hemoglobin, or re-appearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), major adverse vascular events (including thrombosis), dysphagia, or erectile dysfunction. If signs and symptoms of hemolysis occur after discontinuation, including elevated LDH, consider restarting appropriate treatment.

Immunogenicity Leading to Loss of Exposure and Efficacy

Patients may develop anti-drug antibodies (ADAs) that can interfere with Piasky exposure (see section *“Undesirable effects”)*. Development of ADAs may lead to loss of Piasky exposure, which may subsequently result in loss of Piasky efficacy. Loss of efficacy and loss of exposure resulting from ADA development has been observed in patients treated with Piasky in clinical trials. Patients should be monitored 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 vs 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 medical attention if the patient develops signs of worsening PNH.

Further Information

This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. it is nearly "sodium-free".

Interactions

Effects of other substances on the pharmacokinetics of Crovalimab

No dedicated drug-drug interaction studies were conducted. Piasky is not expected to show pharmacokinetic interactions with other drugs interfering with the metabolizing cytochrome P450 (CYP) enzymes, since the clearance pathways of immunoglobulins are distinct from those of small molecules.

Crovalimab and other C5 inhibitors bind different epitopes on C5 such that immune complexes comprised of the antibodies bridged by C5 may form when both are present in the circulation. These immune complexes, also referred to as drug-target-drug complexes (DTDCs), can comprise one or more units of C5 bound to both crovalimab and to another C5 inhibitor and are expected to be cleared within approximately 8 weeks (in the case of eculizumab). The immune complexes may be cleared after a longer duration in the case of switch from C5 inhibitors with an extended half-life such as ravulizumab. In some patients, the formation of these complexes results in Type III immune complex reactions (see "*Warning and Precautions, General*" and "*Undesirable effects*"). In patients switching from another C5 inhibitor therapy, a transient increase in clearance is observed due to the formation of the immune complexes, leading to a faster elimination of crovalimab. However, this transient increase in clearance is not clinically relevant and does not require dose adjustment in patients switching from another C5 inhibitor.

Effects of Crovalimab on the pharmacokinetics of other substances

No dedicated drug-drug interaction studies with other medicinal products were conducted.

Pregnancy, lactation

Females and Males of Reproductive Potential

If Piasky is prescribed to a woman of childbearing potential, she should be advised to contact her physician if she intends to become, or suspects that she is pregnant (see section *"Pregnancy"*).

Pregnancy

No clinical studies of Piasky in pregnant women have been performed.

In studies with pregnant monkeys, no adverse effects were observed (see section *"Preclinical Data")*.

Human immunoglobulin G is known to cross the placental barrier and, as a result, crovalimab can potentially cause terminal complement inhibition in fetal circulation. Piasky should therefore only be given to a pregnant woman if this is clearly necessary.

Labor and Delivery

The safe use of Piasky during labor and delivery has not been established.

Lactation

It is not known whether Piasky is excreted in human breast milk. A risk to the child cannot be ruled out. The healthcare provider and patient should consider the developmental and health benefits of breastfeeding along with the mother's clinical need for Piasky and any potential adverse effects on the breastfed child from Piasky administration or from the underlying maternal condition.

Fertility

No effects on the female or male reproductive organs were observed (see *"Preclinical data"*).

Effects on ability to drive and use machines

Piasky has no or negligible influence on the ability to drive and use machines. No appropriate studies have been conducted.

Undesirable effects

Summary of the safety profile

The safety of crovalimab in patients with PNH was investigated in three Phase III studies, COMMODORE 2 (BO42162), COMMODORE 3 (YO42311) and COMMODORE 1 (BO42161), as well as in one Phase I/II study (COMPOSER, BP39144).

The most common adverse reactions observed in the three Phase III studies were Type III immune complex mediated reaction (18.9% in patients who switched from treatment with another C5 inhibitor to crovalimab), upper respiratory tract infection (18.6%), pyrexia (13.5%), headache (10.9%) and infusion- related reaction (10.2%). The most common serious adverse reactions observed were Type III immune complex mediated reaction (4.0% in patients who switched from treatment with another C5 inhibitor to crovalimab) and pneumonia (1.5%).

The safety results for the 44 patients in the COMPOSER study, with a median duration of treatment of 4.69 years (range: 0.4 - 6.3 years), revealed no additional safety concerns associated with the long-term use of crovalimab.

Summary of adverse drug reactions from clinical trials

Table 2 summarizes the adverse drug reactions (ADRs) that have been reported with the use of Piasky based on a pooled analysis of safety data from COMMODORE 2, COMMODORE 3, and COMMODORE 1 (N=393). The median treatment duration for Piasky was 64 weeks (range: 0.1 – 136.4 weeks) based on the pooled analysis of 393 patients.

ADRs are listed by MedDRA system organ class: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 2 Summary of Adverse Drug Reactions Occurring in Patients Treated with Piasky

Adverse Drug Reactions (MedDRA)	Frequency n = 393*	Frequency Category
General disorders and administration site conditions		
Pyrexia	53 (13.5%)	Very Common
Fatigue		Common
Asthenia		Common
Injection site reaction		Uncommon
Immune system disorders		
Type III immune complex mediated reaction*	38 (18.9%)*	Very Common
Hypersensitivity		Common
Infections and infestations		
Upper respiratory tract infection	73 (18.6%)	Very common
Urinary tract infection		Common
Nasopharyngitis		Common

Pneumonia		Common
Respiratory tract infection		Common
Pyelonephritis		Uncommon
Sepsis		Uncommon
Bacteraemia		Uncommon
Septic shock		Uncommon
Injury, poisoning and procedural complications		
Infusion related reaction	40 (10.2%)	Very common
Injection related reaction		Common
Musculoskeletal and connective tissue disorders		
Arthralgia		Common
Gastrointestinal disorders		
Diarrhoea		Common
Abdominal pain		Common
Nervous system disorders		
Headache	43 (10.9%)	Very common
Skin and subcutaneous tissue disorders		
Rash		Common

* Type III immune complex mediated reaction (also referred to as Type III immune complex reaction) is limited to patients who switch from another C5 inhibitor to crovalimab or from crovalimab to another C5 inhibitor. The frequency of Type III immune complex reactions is reported for a subset of n=201 patients who switched from treatment with another C5 inhibitor to crovalimab, with incidence rates being calculated using these n=201 patients as the denominator.

Description of selected adverse events from clinical trials

Type III immune complex reactions

(see section *"Interactions"*)

Across Phase III studies, 19.4% (39 out of 201) patients who switched from treatment with eculizumab or ravulizumab to Piasky) experienced a Type III immune complex reaction. Of these 39 patients, 2 patients experienced a second Type III immune complex reaction after discontinuing Piasky and switching to ravulizumab. The most common signs and symptoms that were reported were arthralgia and rash, with other reported symptoms including pyrexia, headache, myalgia, abdominal pain, asthenia/fatigue and axonal neuropathy. No renal manifestations of Type III immune complex reactions were reported. The median time to onset of Type III immune complex reactions in patients who switched from treatment with eculizumab or ravulizumab to Piasky was 1.6 weeks (range: 0.7 – 4.4 weeks), whereby 5.1 % of patients (2 of 39) suffered a Type III immune complex reaction with a time to onset exceeding 4 weeks. Most cases of Type III immune complex reaction were transient with a median duration of 1.7 weeks (range 0.4 - 34.1 weeks). The majority of events were Grade 1-2, whereby Grade 3 events occurred in 8 % (16 of 39) of patients treated with crovalimab who had been switched from eculizumab or ravulizumab-resolved with no change in study treatment with Piasky.

In the COMPOSER study, among 26 patients who switched from eculizumab to Piasky, 2 patients reported in total 2 adverse events of Type III immune complex reactions. These events were mild/moderate and non-serious. One additional patient developed a mild Type III immune complex reaction after discontinuing Piasky and switching to a different C5 inhibitor.

Immunogenicity

Across two randomized Phase III studies (COMMODORE 1 and COMMODORE 2) and one single-arm Phase III trial (COMMODORE 3), ADA status was evaluable in 392 patients. Out of these 392 patients, 118 (30.1%) were ADA-positive. The overall safety profile of Piasky was generally consistent between ADA-positive and ADA-negative patients. There was no evidence for a clinical impact of ADA status on the safety profile of Piasky (see section *"Warnings and Precautions, Immunogenicity"*).

Immunogenicity leading to loss of exposure and efficacy

Out of the 392 patients evaluated for ADA status, partial or complete loss of exposure associated with ADA onset was observed in 23 patients (5.9%); among them, 17 (4.3%) had a loss of

pharmacological activity coinciding with a loss of exposure and with loss of efficacy, manifesting as a sustained loss of hemolysis control in 7 patients (1.8%).

Patients may develop ADAs that can interfere with Piasky exposure. In case of clinical signs of loss of efficacy, prompt evaluation by a physician should be sought (see section *"Warnings and Precautions*"*,* and *"Properties/Effects*, *Pharmacodynamics, Immunogenicity").*

Infusion and injection-related reactions

An infusion-related reaction occurred in 10.2 % of patients who were treated with Piasky across Phase III studies. The most common signs and symptoms that were reported were headache (7.1 %), rash (0.8 %), dizziness (0.8 %), abdominal pain (0.5 %), erythema (0.5 %), nausea (0.5 %), pyrexia (0.5 %) and paraesthesia (0.3 %). All reported events were Grade 1 to 2.

Injection-related reactions occurred in 8.4 % of patients who were treated with Piasky across Phase III studies. The most common signs and symptoms that were reported were headache (2.5 %), injection site erythema (1.0 %), injection site pain (1.0 %), and injection site rash (1.0 %). The majority of events were Grade 1 to 2.

Infections with encapsulated bacteria

Based on its mechanism of action, the use of crovalimab may potentially increase the risk of infections, particularly infections caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenza* (see "*Warnings and precautions*").

Across all Phase III studies, infections with encapsulated bacteria that were reported were Klebsiella pneumoniae, Klebsiella (not otherwise specified), *Haemophilus influenzae* and *Neisseria subflava*, the latter of which caused an adverse event of bacteraemia in a patient.

Children and adolescents

In 12 paediatric PNH patients with a body weight ≥ 40 kg (aged 13-17 years old) included in COMMODORE 1, COMMODORE 2 and COMMODORE 3 studies, the safety profile appeared similar to that observed in adult PNH patients. The adverse reactions associated with crovalimab that were reported in paediatric PNH patients are upper respiratory tract infection (16.7 %), urinary tract infection (16.7 %), fatigue (16.7 %), pyrexia (16.7 %), headache (8.3 %), infusion-related reaction (8.3 %) and injection-related reaction (8.3 %).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious side effect online via the EIViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no experience with overdosage of Piasky in human clinical trials. No cases of overdose have been reported.

Properties/Effects

ATC code

L04AJ07

Mechanism of action

Piasky is a recombinant humanized immunoglobulin G1 (IgG1)-based monoclonal antibody that specifically binds with high affinity to component 5 (C5) of the complement system, inhibiting its cleavage into C5a and C5b and thus preventing the formation of the membrane attack complex (MAC). Piasky causes terminal complement activity inhibition. In patients with PNH, Piasky inhibits terminal complement-mediated intravascular hemolysis.

Pharmacodynamics

In clinical studies with PNH patients, a concentration-dependent inhibition of terminal complement activity following treatment with Piasky was observed. Terminal complement activity (CH50 as measured by Liposome Immunoassay [LIA]) inhibition was achieved immediately by the end of the initial Piasky infusion and was sustained through the duration of Piasky treatment. Similarly, mean free C5 concentrations dropped to low levels (<0.0001 g/L) in comparison to baseline and remained low throughout the treatment period.

Free C5 and CH50 levels were similar between pediatric and adult patients treated with Piasky.

Clinical efficacy

The safety and efficacy of Piasky in patients with PNH were evaluated in a non-inferiority Phase III study (COMMODORE 2, BO42162), supported by clinical evidence from two additional Phase III studies (COMMODORE 3, YO42311, and COMMODORE 1, BO42161) and one Phase I/II study (COMPOSER, BP39144).

In all phase III studies, patients were required to be vaccinated against *Neisseria meningitidis*, either within 3 years prior to the start of treatment or within 7 days after starting treatment with Piasky. Patients vaccinated within 2 weeks prior to initiating Piasky or after the start of study treatment received appropriate prophylactic antibiotics until at least 2 weeks after the vaccination. Patients with a history of a Neisseria meningitidis infection in the 6 months before screening and up to the first use of the trial preparation were excluded.

Patients with an allogenic bone marrow transplant in their medical history were also excluded.

Piasky was administered in Phase III studies in accordance with the recommended dose described in section "*Dosage and Administration"*. Rescue doses of 340 mg of Piasky administered intravenously were allowed based on the investigators' judgment if a patient experienced signs and symptoms of PNH; however, these studies were not designed to evaluate the impact of rescue dosing on the efficacy of Piasky.

The Phase III studies consisted of a primary treatment period of 24 weeks, after which patients had the option to continue/switch to Piasky in an extension period.

COMMODORE 2 (Study BO42162)

COMMODORE 2 was a Phase III, randomized, open-label, active-controlled, multicenter clinical study designed to evaluate the efficacy and safety of Piasky compared to eculizumab in patients with PNH not previously treated with a complement inhibitor. 204 patients (body weight ≥ 40 kg) were randomized 2:1 to receive either Piasky (n = 135) or eculizumab (n = 69). The study additionally enrolled 6 pediatric patients (aged < 18 years and with body weight ≥ 40 kg) in a descriptive arm to receive Piasky *(see section* "*Children and adolescents")*. Eligible patients had high disease activity at screening, demonstrated by LDH level ≥ 2 x upper limit of normal (ULN) and by the presence of one or more PNH-related signs or symptoms in the past 3 months : fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia (haemoglobin < 10 g/dl), a history of major adverse vascular event (including thrombosis), dysphagia or erectile dysfunction; or a packed red blood cell (pRBC) transfusion due to PNH in their medical history. Randomization was stratified by the most recent LDH value (≥ 2 to ≤ 4 x ULN, or > 4 x ULN) and by transfusion history (0, > 0 to ≤ 6, or > 6 packed red blood cell (pRBC) units administered within 6 months prior to randomization).

Demographics and baseline characteristics of the randomized study population were generally balanced between the treatment arms and are presented in Table 3.

Table 3 Demographics and Baseline Characteristics for COMMODORE 2 (Randomized Population)

Parameters	Eculizumab (n = 69)	Piasky (n = 135)
Age (years) at PNH diagnosis		
Mean (SD)	37.4 (16.4)	35.8 (15.5)
Median (Range)	32.1 (11.2 – 76.8)	31.0 (11.5 – 74.7)
Age (years) at first administration of the study drug*		
Mean (SD)	41.9 (16.0)	40.5 (15.2)
Median (Range)	38.0 (17-78)	36.0 (18-76)
<18 years, n (%)	2 (2.9)	0
18 - 64 years, n (%)	58 (84.1)	122 (90.4)
≥65 years, n (%)	9 (13.0)	13 (9.6)
Weight		
40 - <100 kg, n (%)	66 (95.7)	131 (97.0)
≥100 kg (n %)	3 (4.3)	4 (3.0)
Sex		
Male, n (%)	35 (50.7)	77 (57.0)
Female, n (%)	34 (49.3)	58 (43.0)
LDH levels at baseline (x ULN)		
Median (range)	7.7 (2.0- 20.3)	7.0 (2.0-16.3)
History of pRBC transfusions in the 12 months prior to screening		
Yes, n (%)	50 (73.5)	103 (77.4)
pRBC units transfused in the 12 months prior to screening		
Median (range)	3.0 (0-41.0)	3.8 (0- 43.5)
Total PNH granulocyte clone size (%)		
Median (Range)	91.4 (5.8 - 100)	93.6 (6.8 - 99.9)
Total PNH monocyte clone size (%)		
Median (Range)	90.9 (42.5 - 99.9)	95.1 (41.5 - 99.9)
Total PNH erythrocytes clone size (%)		
Median (Range)	25.3 (3.5 - 96.0)	44.6 (0.1 – 88.9)

Haemoglobin levels at baseline (g/L) Median (IQR)	85.0 (77.0 - 93.0)	87.0 (81.0 - 97.0)
History of aplastic anemia Yes, n (%)	26 (37.7)	53 (39.3)
History of myelodysplastic syndrome Yes, n (%)	6 (8.7)	6 (4.4)
History of Major Adverse Vascular Event (MAVE) Yes, n (%)	10 (14.5)	21 (15.6)
Medications at baseline**		
Anticoagulants, n (%)	17 (24.6)	35 (25.9)
Steroids, n (%)	25 (36.2)	46 (34.1)
Immunosuppressive therapy, n (%)	13 (18.8)	23 (17.0)

* Two adolescent patients (both 17 years of age) were randomized into the eculizumab arm prior to the opening of the separate descriptive pediatric arm. Both patients switched to Piasky in the extension period after completing the primary treatment period; one patient was still < 18 years, while the other patient had turned 18 years at the time of first Piasky treatment.

** Includes medications that were started prior to initiation of study treatment and were either stopped before or were ongoing at time of initiation of study treatment.

The primary objective of the study was to evaluate the efficacy of Piasky compared with eculizumab, based on the non-inferiority (NI) assessment of the following co-primary endpoints: hemolysis control, as measured by the mean proportion of patients with LDH ≤ 1.5 x ULN from Week 5 to Week 25; and the proportion of patients who achieved transfusion avoidance (TA), defined as patients who are pRBC transfusion-free, from baseline through Week 25. Secondary efficacy endpoints included the proportion of patients with breakthrough hemolysis, proportion of patients with stabilized hemoglobin, and change in fatigue (measured by the FACIT-Fatigue scale) from baseline to Week 25. Breakthrough hemolysis was defined as at least one new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥ 2 x ULN after prior reduction of LDH to ≤ 1.5 x ULN on treatment. Hemoglobin stabilization was defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline, in the absence of transfusion.

Piasky was non-inferior to eculizumab for both co-primary endpoints of hemolysis control and transfusion avoidance and for the secondary endpoints of hemoglobin stabilisation and breakthrough haemolysis (Table 4). Due to the break in the statistical testing hierarchy, non-inferiority testing for FACIT-Fatigue was not performed and the results are considered descriptive only.

Table 4 Efficacy Results from COMMODORE 2 (Primary Analysis Population)

	Eculizumab (n = 69)	Piasky (n = 134)[a]
Co-Primary Efficacy Endpoints		
Proportion of patients with Transfusion Avoidance, % (95% CI)	68.1 (55.7, 78.5)	65.7 (56.9, 73.5)
Difference in proportions[b], % (95% CI)[e]	-2.8% (-15.7, 11.1)	
Mean proportion of patients achieving hemolysis control, % (95% CI)	79.0 (69.7, 86.0)	79.3 (72.9, 84.5)
Odds Ratio[c] (95% CI)[e]	1.02 (0.57, 1.82)	
Secondary Efficacy Endpoints		
Proportion of patients with Breakthrough Hemolysis[b], % (95% CI)	14.5 (7.5, 25.5)	10.4 (6.0, 17.2)
Difference in proportions[b], % (95% CI)[e]	- 3.9 (-14.8, 5.3)	
Proportion of patients with stabilized hemoglobin, (95% CI)	60.9 (48.4, 72.2)	63.4 (54.6, 71.5)
Difference in proportions[b], % (95% CI)[e]	2.2 (-11.4, 16.3)	
Adjusted mean change from baseline in FACIT-Fatigue at Week 25, (95% CI)[d]	5.2 (3.4, 6.9)	7.8 (6.5, 9.1)

Difference in adjusted mean[b], (95% CI)	2.6 (0.7, 4.6)

CI = confidence interval; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy Fatigue

[a]* One patient randomized to Piasky did not have post-baseline LDH and was not included in the primary efficacy analysis.

[b] Difference calculated as Piasky minus eculizumab

[c] Odds ratio calculated as odds for Piasky divided by odds for eculizumab

[d] Due to the break in the statistical testing hierarchy, non-inferiority testing for FACIT-Fatigue was not performed and the results are considered descriptive only.

[e] Non-inferiority was demonstrated based on the margin pre-specified in the study protocol

COMMODORE 1 (Study BO42161)

COMMODORE 1 was a Phase III, randomized, open-label, active-controlled, multicenter clinical study evaluating the safety, pharmacodynamics, pharmacokinetics and exploratory efficacy of Piasky in patients switching from another C5 inhibitor therapy.

The primary aim of the study was the assessment of safety. Efficacy data are descriptive.

89 patients switching from approved doses of eculizumab and with hemolysis control at screening (LDH level ≤1.5 x ULN), were randomized 1:1 to receive either Piasky (n = 45) or eculizumab (n = 44). Patients were excluded if they had suffered a serious major adverse vascular event (MAVE) within 6 months prior to the first administration of the investigational product.

Demographics and baseline characteristics of the randomized study population were generally balanced between the treatment arms. The 45 patients randomized to the Piasky arm had a median age of 42.0 years (range: 21-81 years), with 53.3% of the patients being female. Of the 44 patients randomized to the eculizumab arm, the median age was 49.0 years (range: 22 - 85 years) with 50.0% being female. The median LDH value at baseline was 1.01 × ULN (range: 0.6- 1.7) for Piasky and 0.96 × ULN (range: 0.7- 1.9) for eculizumab. The proportion of patients with a history of transfusions in the 12 months prior to screening was 22.7% in the Piasky arm and 25% in the eculizumab arm, with a mean (SD) of 1.6 (3.7) units of transfused pRBC and 2.3 (5.4) in the Piasky and eculizumab arms respectively.

An exploratory evaluation of the efficacy was carried out in 76 of 89 randomized patients (n = 39 for crovalimab and n = 37 for eculizumab) who had been enrolled in the study at least 24 weeks before the cut-off date for the primary analysis.

The mean proportion of patients maintaining hemolysis control from baseline through Week 25 was 92.9% [95% CI: 86.6, 96.4] for patients randomized to Piasky and 93.7% [95% CI: 87.3, 97.0] for patients randomized to eculizumab. Transfusion avoidance was observed in 79.5% [95% CI: 63.1, 90.1] of patients randomized to Piasky and 78.4% [95% CI: 61.3, 89.6] of patients randomized to eculizumab.

Children and adolescents

Efficacy was evaluated in a limited number of pediatric patients (n=12; with body weight ≥ 40 kg treated with Piasky in COMMODORE 1 (n=2), COMMODORE 2 (n=7), and in COMMODORE 3 (n=3).

Nine pediatric patients were treatment-naïve, two patients switched from standard dose eculizumab and one patient switched from ravulizumab. All pediatric patients received the same dosing as adult

patients based on body weight as outlined in section "*Dosage/Administration*/*Dose Recommendation*" (see "*Properties/Effects, Children and adolescents*"). Hemolysis control (defined as LDH ≤1.5 x ULN) from baseline to Week 25 was achieved in 7 of the 9 patients who were treatment-naïve, and the 3 patients switching from eculizumab or ravulizumab to Piasky maintained hemolysis control through 24 weeks of Piasky treatment. Nine (six patients who were treatment-naïve and three patients who switched from eculizumab or ravulizumab) out of the 12 pediatric patients achieved transfusion avoidance and hemoglobin stabilization, and no patients had a breakthrough hemolysis event during the 24-week treatment period.

Immunogenicity

As with all therapeutic proteins, there is the potential for immune response to Piasky.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to Piasky with the incidence of antibodies to other products may be misleading.

In the Phase III study COMMODORE 2, treatment-emergent anti-drug antibodies (ADAs) were observed in 35.0% (49/140) of treatment-naïve patients who received Piasky and 38.2% (26/68) of patients who switched from treatment with another C5 inhibitor to Piasky. The median time to the development of first post-baseline ADAs was 16.1 weeks (range: 1.1 to 72.3 weeks), and 16.6 weeks (range: 2.1 to 36.3 weeks) in the treatment-naïve patients and patients who were previously treated with another C5 inhibitor, respectively. Across Phase III studies, the incidence of treatment-emergent ADAs was 35.1% (67 patients out of 191) and 25.4% (51 patients out of 201) in treatment-naive and patients who switched from treatment with another C5 inhibitor to Piasky, respectively.

Across studies, median concentration time-courses in ADA-positive patients were slightly lower in comparison to ADA-negative patients. Despite this effect, concentrations remained above 100 µg/mL (the threshold for complete terminal complement inhibition) in more than 80% of ADA-positive patients. ADA presence was not associated with clinically meaningful impact on pharmacokinetics, pharmacodynamics, and efficacy in most of the patients; however, 17 (out of 392, 4.3%) ADA-positive patients had a loss pharmacological activity (based on CH50 or free C5) coinciding with a loss of exposure, with loss of efficacy, manifesting as a sustained loss of hemolysis control in 7 patients (1.8%). There was no evidence for a clinical impact of ADA status on the safety profile of Piasky.

Pharmacokinetics

The pharmacokinetics of Piasky have been characterized both in healthy volunteers and in patients with PNH. The pharmacokinetics were characterized using non-linear mixed effects pharmacokinetic analysis methods based on the pooled database composed of 9 healthy volunteers as well as 210 and 211 treatment-naïve patients and patients who switched from previous treatment with another C5 inhibitor to Piasky, respectively, from the following 4 studies: COMMODORE 2 (BO42162), COMMODORE 3 (YO42311), COMMODORE 1 (BO42161) and COMPOSER (BP39144).

The concentration-time course of Piasky is best described using a two-compartment model with first-order elimination and a first-order subcutaneous absorption. To describe the transient increase in clearance due to the formation of immune complexes observed in patients who switched from treatment with another C5 inhibitor to Piasky, an additional time-varying clearance parameter, which decreases exponentially with time, was added. At steady state, exposure is expected to be similar between naïve and switch patients.

Piasky clearance and volume parameters were scaled by body weight. Body weight was shown to be a significant covariate, with clearances and volumes of distribution increasing with body weight. Age was also found as a significant covariate on the absorption rate, with absorption rate decreasing with age.

The recommended dosing regimen uses a flat dosing approach with body weight tiers to compensate for the effect of body weight on Piasky exposure. No dose adjustment was required to compensate for the effect of age on Piasky absorption.

Absorption

The absorption rate constant was estimated to be 0.126 day^{-1} [90 % CI: 0.105, 0.176]. Following subcutaneous administration, the bioavailability was estimated at 83.0 % [90% CI: 69.6 % - 92.0 %].

Distribution

The central volume of distribution was estimated to be 3.23 L (90% CI: 3.16, 3.29) and the peripheral volume of distribution was estimated as 2.32 L (90% CI: 2.02, 2.67). The inter-compartmental clearance was 0.186 L/day (90% CI: 0.138, 0.221).

The small volume of distribution indicates that Piasky is likely to be distributed mainly in plasma and/or in vascular rich tissues.

Metabolism

The metabolism of Piasky has not been directly studied. IgG antibodies are mainly catabolized by lysosomal proteolysis and then eliminated from or reused by the body.

Elimination

The clearance was estimated to be 0.0791 L/day (90% CI: 0.0678, 0.0872). The terminal half-life estimated was 53.1 days (90% CI: 47.7, 58.6). This longer half-life is consistent with recycling properties of Piasky.

Pharmacokinetic Profile at Steady State

Secondary pharmacokinetics parameters at steady state for patients enrolled in the Phase III study COMMODORE 2, were derived using the population pharmacokinetic model. Steady-state serum Piasky concentrations were achieved approximately 12 weeks following the first dose. These parameters are summarized in Table 5.

Table 5 Secondary Pharmacokinetic Parameters at Steady State Derived from the Population Pharmacokinetic Model for PNH patients randomized to treatment with Piasky in COMMODORE 2

Parameter	Mean	SD	Median	Minimum	Maximum
$C_{max,ss}$ (µg/mL)	303	86.7	303	62.2	545
$t_{max,ss}$ (days)	8.14	0.857	8.20	5.29	11.2
$AUC_{\tau,ss}$ (µg/mL · days)	7810	2260	7830	1560	14400
$C_{trough,ss}$ (µg/mL)	241	72.7	239	44.0	465
$C_{av,ss}$ (µg/mL)	279	80.9	279	55.7	515

$AUC_{\tau,ss}$ = area under the concentration-time curve for a dosing interval at steady state;
$C_{max,ss}$ = maximum concentration during a dosing interval at steady state;
$C_{av,ss}$ = average concentration at steady state; $C_{trough,ss}$ = trough concentration at steady state;
$t_{max,ss}$ = time after most recent dose to reach the maximum concentration at steady state;
SD = standard deviation. Parameters are displayed only for patients reaching steady state conditions.

Pharmacokinetics of special populations

No pharmacokinetic studies with Piasky have been conducted in special populations.

After inclusion of the bodyweight, the population pharmacokinetic analyses in patients with PNH showed that age (12 to 85 years old), gender and race did not meaningfully influence the pharmacokinetics of Piasky.

Children and adolescents

Data obtained in adolescent patients indicate that exposure in pediatric patients weighing ≥ 40 kg was consistent with that of adult patients.

Elderly patients

No dedicated studies have been conducted to investigate the pharmacokinetics of Piasky in the geriatric population, however the data obtained in PNH clinical studies indicates that exposure in patients aged ≥ 65 years was found to be comparable to that of patients in other age groups.

Renal impairment

No dedicated studies have been conducted to investigate the pharmacokinetics of Piasky in patients with renal impairment, however the data obtained in PNH clinical studies indicate that exposure in patients with mild, moderate, or severe renal impairment were comparable to that of patients without renal impairment.

Hepatic impairment

No dedicated studies have been conducted to investigate the pharmacokinetics of Piasky in patients with hepatic impairment, however the data obtained in PNH clinical studies indicate that exposure in patients with mild hepatic impairment are comparable to that of patients without hepatic impairment.

Preclinical data

Nonclinical data revealed no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and reproductive toxicity.

Genotoxicity

No studies have been performed to establish the genotoxic potential of Piasky.

Carcinogenicity

No carcinogenicity studies have been performed to establish the carcinogenic potential of Piasky.

Fertility

No effects on female or male reproductive organs were observed in cynomolgus monkeys following repeated administration of Piasky for up to 6 months.

Developmental Toxicity

The potential for reproductive toxicity was investigated in an enhanced pre- and post-natal development study in cynomolgus monkeys. Pregnant monkeys were given an intravenous loading dose of 100 mg/kg on gestation day (GD) 20, followed by weekly subcutaneous injections of up to 100 mg/kg up to parturition. The dams and infants were then observed untreated for 6 months. There were no adverse effects of Piasky on pregnancy or on the viability, growth and development of the infants up to 100 mg/kg, providing exposures equivalent to 14-times the human exposure based on AUC.

Other information

Incompatibilities

Intravenous administration

Do not use diluents other than 0.9% sodium chloride solution to dilute Piasky since their use have not been tested.

No incompatibilities have been observed between Piasky and intravenous infusion bags with product-contacting materials made of polyvinyl chloride (PVC), or polyolefins (PO) such as polyethylene (PE) and polypropylene (PP). In addition, no incompatibilities have been observed with infusion sets or infusion aids with product-contacting materials made of PVC, PE, polyurethane (PU), polybutadiene (PBD), acrylonitrile butadiene styrene (ABS), polycarbonate (PC), polyetherurethane (PEU) or polytetrafluorethylene (PTFE).

Subcutaneous administration

No incompatibilities between Piasky and the recommended syringes made of siliconized polycarbonate (PC) or polypropylene (PP), with polyethylene (PE) stoppers and stainless steel injection needles have been observed.

Influence of diagnostic methods

Not applicable.

Shelf life

Shelf-life of unopened vial

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening

Shelf-life of the intravenous infusion of Piasky after dilution

From a microbiological point of view, the diluted solution for intravenous infusion should be used immediately because the medicine does not contain any antimicrobial-preservative.

If the diluted solution is prepared under aseptic conditions, the chemical and physical stability of the medicine have been demonstrated in the refrigerator at 2°C to 8°C and at room temperature (up to 30°C). Detailed storage conditions of the prepared solution for infusion depending on the type of infusion bags used are provided in Table 6.

Table 6 Storage Conditions for the Prepared Solution for Infusion

Infusion bags	Storage conditions
PO/PE/PP	Up to 30 days at 2°C to 8°C protected from light, and up to 24 hours at room temperature (up to 30°C) under ambient light conditions. Protect from direct sunlight.
PVC	Up to 12 hours at 2°C to 8°C protected from light, and up to 12 hours at room temperature (up to 30°C) under ambient light conditions. Protect from direct sunlight.

polyolefins (PO), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC)

Shelf-life of the subcutaneous injection of Piasky after withdrawal from vial

Use aseptic technique when preparing the Piasky syringe for subcutaneous injection.

From a microbiological point of view, Piasky should be injected immediately after transfer from the vial to the syringe, as the medicinal product does not contain antimicrobial preservatives.

If Piasky is transferred from the vial to the syringe under aseptic conditions in a healthcare environment, the chemical and physical stability of the medicine in the capped syringe has been demonstrated in the refrigerator at 2°C to 8°C for up to 14 days protected from light and at room temperature (up to 30°C) for up to 24 hours at ambient light.
Piasky solution must be protected from direct sunlight.

Special precautions for storage

For Piasky vials

Keep out of the reach of children.
Store in the refrigerator (2-8 °C).
Do not shake. Do not freeze.

Keep the container in the outer carton in order to protect the contents from light.
The vial can be stored in the outer carton at below 30°C for up to 7 days.
Prior to administration, if necessary, unopened vials may be stored in the outer carton out of the refrigerator at room temperature, if necessary, and then returned to refrigeration. The total combined time out of the refrigerator should be no more than 7 days and the temperature should not exceed 30°C. Use the boxes on the inner side of the top flap of the outer carton to document the duration of storage out of the refrigerator. Tick one box for each day Piasky is stored without refrigeration. Discard the vial if it has been stored out of the refrigerator at room temperature for any longer than 7 days.

Instructions for handling

Piasky vial is for single use only.

Piasky is a sterile and preservative-free solution that is used undiluted for subcutaneous injection or diluted for intravenous infusion.

Piasky should be inspected visually to ensure there is no particulate matter or discoloration prior to administration. Piasky is clear to strongly opalescent, and almost colorless to brownish-yellow solution. Piasky should be discarded if the medicine looks cloudy, discolored or has particles in it.

Intravenous Administration

Piasky must be prepared by a healthcare provider under aseptic technique. Piasky solution must be diluted in 0.9% (w/v) sodium chloride (NaCl) solution prior to administration. A 0.2 µm in-line filter must be used with the infusion set during administration.

A dedicated infusion line must be used during intravenous administration.

Dilution

1. Withdraw the required volume of Piasky from the vial (see Table 7) using a sterile syringe and dilute into the infusion bag. Multiple vials need to be used to meet the required volume of Piasky to be added to the infusion bag. Discard any unused portion left in the vial.

   Dilution of Piasky in infusion bags containing 0.9% NaCl must be in the range of 4-15 mg/mL (final concentration after dilution).

   Intravenous infusion bags of a volume of 100 mL or 250 mL can be used.

Table 7 Dose example volume determination

Dose (mg)	Concentration in bag (mg/mL)	Volume of Piasky in 0.9% sodium chloride solution* (mL)	Size of infusion bags (mL)
1000	4	5.9	250
1500	6	8.8	250
1000	10	5.9	100
1500	15	8.8	100

* Each 340 mg vial contains a nominal fill volume of 2.0 mL

2. Gently mix the infusion bag by slowly inverting the bag. Do not shake.

3. Inspect the infusion bag for particulates and discard if present.

4. Flushing of infusion line is required in order to ensure complete administration of the entire dose.

Subcutaneous Administration

Piasky should be used undiluted. A syringe, a transfer needle and an injection needle are needed to withdraw Piasky solution from the vial and inject it subcutaneously.

Each injection is of a volume of 2 mL Piasky, corresponding to 340 mg. A 2 mL-size or 3 mL-size syringe should be used for each injection. A dose of 680 mg is achieved by performing two consecutive subcutaneous injections of 340 mg. A dose of 1020 mg is achieved by performing three consecutive subcutaneous injections of 340 mg.

2 mL or 3 mL syringe

Criteria: Transparent polypropylene or polycarbonate syringe with Luer-Lock tip (in case not locally available, a syringe with Luer Slip™ tip can be used), sterile, single-use, latex-free and non-pyrogenic.

Transfer needle

Criteria: Stainless steel, sterile, preferably gauge 18 G with single bevel at approximately 45 degrees to reduce risk of needle stick injury, or gauge 21 G standard needle as an alternative single-use, latex-free and non-pyrogenic. A transfer needle without filter is recommended.

Injection needle

Criteria: Stainless steel, sterile, gauge 25 G, 26 G or 27 G, length 3/8'' to ½'' (9 mm to 13 mm), single-use, latex-free and non-pyrogenic, preferably including safety needle shield.

Disposal of Unused/Expired Medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

Any unused/expired medicinal product or waste material should be disposed of in accordance with local requirements.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused or shared with others.
- Place all used needles and syringes into a sharp container (puncture-proof disposable container).

Marketing authorisation number

69340 (Swissmedic).

Packs

1 vial of 340 mg/2mL Crovalimab, solution for infusions / injections [A].

Marketing authorisation holder

Roche Pharma (Switzerland) Ltd., Basel.

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