Piasky 340 mg®

Solution for injection/infusion
Crovalimab

1 NAME OF THE MEDICINAL PRODUCT

Piasky 340 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL vial contains 340 mg of crovalimab.

Each mL of solution for injection/infusion contains 170 mg crovalimab.

Crovalimab is a humanised monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion (injection/infusion).

Sterile, clear to strongly opalescent and almost colourless to brownish-yellow solution. The solution has a pH of approximately 5.8 and an osmolality of approximately 297 mOsm/kg.

Patient safety information card and Patient safety information guide
The marketing of Piasky is subject to a risk management plan (RMP) including safety information materials ('patient card' and 'patient guide'). These materials emphasize important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review these materials before starting treatment.

Health Care Professional (HCP) guide
This product is marketed with an HCP guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (C5) inhibitor for at least the past 6 months.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of haematological disorders.

Posology

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 (see section 4.4 for additional information related to switching between complement component 5 [C5] inhibitor treatments). 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	1,000 mg (intravenous)	1,500 mg (intravenous)
Day 2, 8, 15, 22	340 mg (subcutaneous)	340 mg (subcutaneous)
Maintenance dose		
Day 29 and Q4W[a] thereafter	680 mg (subcutaneous)	1,020 mg (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). If this occurs, the subsequent dose should be administered according to the regular schedule.

Duration of treatment

Piasky is intended for long-term treatment unless the discontinuation of this medicinal product is clinically indicated (see section 4.4).

Delayed 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 take two doses or administer more than the prescribed dose on the same day to make up for a missed dose.

Dose modifications

Modification of the maintenance dose is required if the patient's body weight changes by 10% or more to become consistently greater than or lower than 100 kg during the course of treatment (see Table 1

for recommended dose). Accordingly, the patient's body weight should be monitored periodically and on an ongoing basis, as appropriate.

Special populations

Elderly

No dose adjustment is required in patients ≥ 65 years of age, although experience with crovalimab in elderly patients in clinical studies is limited (see section 5.2).

Renal impairment

No dose adjustment is recommended for patients with mild, moderate or severe renal impairment (see section 5.2).

Hepatic impairment

No dose adjustment is recommended for patients with mild hepatic impairment. Crovalimab has not been studied in patients with moderate to severe hepatic impairment and no recommendation on posology can be provided (see section 5.2).

Paediatric population

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

Method of administration

Piasky is administered as an intravenous infusion (first dose) and as a subcutaneous injection (subsequent doses).

Intravenous administration

Piasky should be prepared for intravenous administration using appropriate aseptic technique. Piasky must be diluted and administered by a healthcare professional as an intravenous infusion over 60 minutes ± 10 minutes (1,000 mg) or 90 minutes ± 10 minutes (1,500 mg). Piasky should not be administered as an intravenous push or bolus.

For instructions on dilution of the medicinal product before administration, see section 6.6.

The infusion of crovalimab 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 4.4).

Subcutaneous administration

Piasky must be used undiluted and should be prepared using appropriate aseptic technique. It is recommended to inject Piasky into the abdomen. Within the abdomen, injection sites should be rotated with every injection. 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

After proper training in subcutaneous injection technique, the patient may self-administer Piasky or the caregiver may administer Piasky without healthcare professional (HCP) supervision if the treating physician determines that it is appropriate.

Comprehensive instructions for the administration of Piasky are given at the end of the Package Leaflet.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with unresolved *Neisseria meningitidis* infection.
- Patients who are not currently vaccinated against *Neisseria meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

Serious meningococcal infection

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

Meningococcal infection may become rapidly life-threatening or fatal if not recognised 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 crovalimab. If immediate treatment with crovalimab 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 crovalimab 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 vaccinations 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 antibacterial agents 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 treatment with Piasky with the patients and provide them with a patient guide and a patient card. As instructed by annual reminders per local RMP, healthcare professionals will receive a reminder annually to ensure patient vaccinations and should ensure patient vaccinations are kept up to date.

Other systemic infections

Due to its mechanism of action, crovalimab 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 local guidelines mandate vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) infections, this should be performed at least 2 weeks prior receiving the first dose of crovalimab. If immediate treatment with crovalimab 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 crovalimab until 2 weeks after vaccination or according to local standard of care, whichever is longer.

If Piasky is administered to patients with active systemic infections, patients should be monitored closely for signs and symptoms of worsening infection. Patients were excluded from clinical studies with crovalimab if they had any active systemic bacterial, viral, or fungal infection within 14 days prior to starting treatment.

Patients should be provided with information from the package leaflet to increase their awareness of the signs and symptoms of potential serious infections.

Type III immune complex reactions

Immune complex formation occurs in patients switching between complement inhibitors which bind different epitopes (see section 4.5). In some patients, the formation of these complexes can result in Type III immune complex mediated reactions, also referred to as Type III immune complex 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 treatment have passed since the last dose) are not at risk of Type III immune complex reactions. Clinical studies with crovalimab reported adverse events of Type III immune complex mediated reactions (see section 4.8).

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

Based on time-to-onset for Type III immune complex reactions observed in clinical studies, it is recommended that patients are monitored for the first 30 days after switching from eculizumab or ravulizumab to crovalimab (or vice-versa) 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 parenteral corticosteroid therapy can be initiated and tapered as clinically indicated.

Infusion and injection-related reactions

Administration of crovalimab 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 such as headache or muscle pain.

In the event of a severe infusion-related reaction after intravenous Piasky administration, treatment should be interrupted and appropriate medical therapy should be administered. In the event of a severe injection-related reaction after subcutaneous administration or any incidence of serious allergic reaction following intravenous or subcutaneous administration, patients/caregivers should seek immediate medical attention and appropriate medical therapy should be administered. Patients should confirm with their healthcare professional whether treatment with Piasky can be continued.

Serious haemolysis after treatment discontinuation in PNH patients

In case of Piasky discontinuation, patients who do not switch to another treatment for PNH must be closely monitored for signs and symptoms of serious intravascular haemolysis, identified by elevated lactate dehydrogenase (LDH) levels, along with sudden decrease in PNH clone size or haemoglobin, or re-appearance of symptoms such as fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), major adverse vascular events (including thrombosis), dysphagia, or erectile dysfunction. If signs and symptoms of haemolysis 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 crovalimab exposure. Development of ADAs may lead to loss of crovalimab exposure, which may subsequently result in loss of crovalimab efficacy. Loss of efficacy and loss of exposure resulting from ADA development has been observed in patients treated with crovalimab in clinical studies. Patients should be routinely monitored for clinical signs of loss of exposure and efficacy, including serious intravascular haemolysis. 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. See sections 4.8 and 5.1.

4.5 Interaction with other medicinal products and other forms of interaction

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 sections 4.4 and 4.8). 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.

No dedicated interaction studies have been conducted.

Crovalimab is not expected to show pharmacokinetic interactions with other medicinal products interfering with the metabolising cytochrome P450 (CYP) enzymes, since the clearance pathways of immunoglobulins G (IgGs) are distinct from those of small molecules.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no data from the use of crovalimab in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Human IgG is known to cross the placenta after first trimester of pregnancy. Based on its mechanism of action, crovalimab may potentially cause terminal complement inhibition in the foetal circulation.

Therefore, the use of Piasky may be considered in pregnant women if the clinical condition of the woman requires treatment with crovalimab.

Breast-feeding

It is not known whether crovalimab is excreted into human breast milk. Human IgG1 is known to be excreted in human milk. A risk to the breastfed infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue from Piasky therapy taking into account the benefit of breast-feeding for the infant and the benefit of therapy for the mother.

Fertility

No clinical data are available on the effect of crovalimab on human fertility. Animal data from repeated-dose toxicity studies showed no effect on male or female reproductive organs (see section 5.3).

4.7 Effects on ability to drive and use machines

Piasky has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions observed 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 from the 44 patients in the COMPOSER study where the median treatment duration was 4.69 years (range: 0.4 - 6.3 years) did not reveal any additional safety concerns associated with long term use of crovalimab.

Tabulated list of adverse reactions

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

Table 2 lists the adverse reactions that have been reported in association with the use of crovalimab in a pooled analysis of 393 patients enrolled in the Phase III studies, unless otherwise stated. The median treatment duration for crovalimab based on the pooled analysis of 393 patients was 64 weeks (range: 0.1 - 136.4 weeks).

Adverse reactions are listed by MedDRA system organ class. The corresponding frequency category for each adverse reaction is based on the following convention: 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). Within each frequency category, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Summary of adverse reactions occurring in patients treated with Piasky

MedDRA system organ class	Adverse reactions (MedDRA)	Frequency category
Infections and infestations	Upper respiratory tract infection	Very common
	Pneumonia	Common
	Respiratory Tract Infection	
	Urinary Tract Infection	
	Nasopharyngitis	
	Sepsis	Uncommon
	Septic shock	
	Bacteraemia	
	Pyelonephritis	
Immune system disorders	Type III immune complex mediated reaction*	Very common
	Hypersensitivity	Common
Nervous system disorders	Headache	Very common
Gastrointestinal Disorders	Abdominal pain	Common
	Diarrhoea	
Skin and subcutaneous tissue disorders	Rash	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Common
General disorders and administration site conditions	Pyrexia	Very common
	Asthenia	Common
	Fatigue	
	Injection site reaction	Uncommon
Injury, poisoning and procedural complications	Infusion related reaction	Very common
	Injection-related reaction	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. See below.

Description of selected adverse reactions

Type III immune complex reactions (see sections 4.4 and 4.5)

Across Phase III studies, 19.4% (39 out of 201) of patients who switched from treatment with eculizumab or ravulizumab to crovalimab experienced a Type III immune complex reaction (reported as Type III immune complex mediated reaction). Of these 39 patients, 2 patients experienced a second Type III immune complex reaction after discontinuing crovalimab and switching to ravulizumab. The most common signs and symptoms that were reported were arthralgia and rash, and other symptoms reported include pyrexia, headache, myalgia, abdominal pain, asthenia/fatigue and axonal neuropathy. The median time to onset of a Type III immune complex reaction in patients who switched from treatment with eculizumab or ravulizumab to crovalimab was 1.6 weeks (range: 0.7 - 4.4 weeks), with 5.1% of patients (2 of 39) experiencing a Type III immune complex reaction with a time to onset that exceeded 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 patients experienced a Grade 1 or 2 event (23 of 39 patients), with Grade 3 events affecting 8% (16 of 39) of crovalimab-treated patients who switched from eculizumab or ravulizumab. Most events resolved with no change in study treatment with crovalimab.

In the COMPOSER study, among 26 patients who switched from eculizumab to crovalimab, 2 patients each reported 1 adverse event of Type III immune complex reaction. These events were mild/moderate and non-serious. One additional patient developed a mild Type III immune complex reaction after discontinuing crovalimab and switching to a different C5 inhibitor.

Immunogenicity

Across two randomised Phase III studies (COMMODORE 1 and COMMODORE 2) and one single-arm Phase III study (COMMODORE 3), ADA status was evaluable in 392 patients. Out of these 392 patients, 118 (30.1%) were ADA-positive. No differences in the rates of adverse reactions typically associated with immunogenicity (such as infusion-related reactions, injection site reactions, or hypersensitivity) were observed between ADA-positive and ADA-negative patients (see section 5.1).

Immunogenicity leading to loss of exposure and efficacy

Patients may develop ADAs that can interfere with crovalimab exposure. Out of 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 haemolysis control in 7 patients (1.8%).

In case of clinical signs of loss of efficacy, prompt evaluation by a healthcare professional should be sought (see section 4.4).

Infusion and Injection-Related Reactions

Across Phase III studies, 10.2% of patients who were treated with crovalimab experienced an infusion related reaction. 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 events reported were Grade 1-2.

Across Phase III studies, 8.4% of patients who were treated with crovalimab experienced an injection-related reaction. 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 1-2.

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 influenzae* (see section 4.4).

Across 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 bacteriaemia in a patient.

Paediatric population

In 12 paediatric PNH patients with 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/.

4.9 Overdose

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Complement inhibitors, ATC code: L04AJ07

Mechanism of action

Crovalimab is a recombinant humanised 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). Crovalimab causes terminal complement activity inhibition. In patients with PNH, crovalimab inhibits terminal complement-mediated intravascular haemolysis.

Pharmacodynamic effects

In clinical studies with PNH patients, a concentration-dependent inhibition of terminal complement activity following treatment with crovalimab was observed. Terminal complement activity (CH50 as measured by Liposome Immunoassay [LIA]) inhibition was achieved immediately by the end of the initial crovalimab infusion and was generally sustained through the duration of crovalimab treatment.

Similarly, mean free C5 concentrations decreased 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 paediatric and adult patients treated with crovalimab.

Clinical efficacy and safety

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

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 crovalimab. Patients vaccinated within 2 weeks prior to initiating crovalimab or after the start of study treatment received appropriate prophylactic antibiotics from the time they started Piasky until at least 2 weeks after the vaccination (see section 4.4 for warnings and precautions related to serious meningococcal infection). Patients with a history of *Neisseria meningitidis* infection in the 6 months prior to screening and up to the first study drug administration were excluded.

Patients were also excluded if they had a history of allogenic bone marrow transplantation.

Crovalimab was administered in Phase III studies in accordance with the recommended dose described in section 4.2. Rescue doses of 340 mg of crovalimab administered intravenously were allowed based on the investigators' judgement 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 crovalimab. Eculizumab was administered per local prescribing information, or in a country without access to commercial eculizumab (COMMODORE 2), then eculizumab 600 mg was given intravenously once weekly for the first 4 weeks, followed by 900 mg every 2 weeks thereafter. Rescue doses of eculizumab were not allowed on study.

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

Study in complement inhibitor-naïve patients with PNH

COMMODORE 2 (Study BO42162)

COMMODORE 2 was a Phase III, randomised, open-label, active-controlled, multicentre clinical study designed to evaluate the efficacy and safety of crovalimab compared to eculizumab in patients with PNH who were not previously treated with a complement inhibitor. 204 patients (body weight ≥ 40 kg), were randomised 2:1 to receive either crovalimab (n = 135) or eculizumab (n = 69). The study additionally enrolled 6 paediatric patients (aged < 18 years and with body weight ≥ 40 kg) in a descriptive arm to receive crovalimab (see section 5.1). Eligible patients had high disease activity at screening, demonstrated by LDH level ≥ 2 × 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, shortness of breath (dyspnoea) anaemia (haemoglobin < 10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of packed red blood cell (pRBC) transfusion due to PNH.

Randomisation was stratified by the most recent LDH value (≥ 2 to ≤ 4 × ULN, or > 4 × ULN) and by the transfusion history (0, > 0 to ≤ 6, or > 6 pRBC units administered within 6 months prior to randomisation); the respective stratification categories were balanced across treatment arms.

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

Table 3: Demographics and baseline characteristics for COMMODORE 2 (randomised population)

Parameters	Crovalimab (N= 135)	Eculizumab (N= 69)
Age (years) at PNH diagnosis		
Mean (SD)	35.8 (15.5)	37.4 (16.4)
Median (Range)	31.0 (11.5 – 74.7)	32.1 (11.2 - 76.8)
Age (years) at first administration of the study treatment*		
Mean (SD)	40.5 (15.2)	41.9 (16.0)
Median (Range)	36.0 (18 – 76)	38.0 (17 – 78)
< 18 years (n, %)	0	2 (2.9%)
18 – 64 years (n, %)	122 (90.4%)	58 (84.1%)
≥ 65 years (n, %)	13 (9.6%)	9 (13.0%)
Weight		
40 – < 100 kg (n, %)	131 (97.0%)	66 (95.7%)
≥ 100 kg (n, %)	4 (3.0%)	3 (4.3%)
Sex		
Male (n, %)	77 (57.0%)	35 (50.7%)
Female (n, %)	58 (43.0%)	34 (49.3%)
LDH levels at baseline (x ULN)		
Median (Range)	7.0 (2.0 -16.3)	7.7 (2.0 - 20.3)
History of pRBC transfusions in the 12 months prior to screening		
Yes (n, %)	103 (77.4%)	50 (73.5%)
pRBC units transfused in the 12 months prior to screening		
Median (Range)	3.8 (0 - 43.5)	3.0 (0 - 41.0)
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 anaemia		
Yes (n, %)	53 (39.3%)	26 (37.7%)
History of myelodysplastic syndrome		
Yes (n, %)	6 (4.4%)	6 (8.7%)
History of Major Adverse Vascular Event (MAVE)		
Yes (n, %)	21 (15.6%)	10 (14.5%)
Medicinal products at baseline**		
Anticoagulants (n, %)	35 (25.9%)	17 (24.6%)
Steroids (n, %)	46 (34.1%)	25 (36.2%)
Immunosuppressive therapy (n, %)	23 (17.0%)	13 (18.8%)
PNH-related signs or symptoms within 3 months prior to screening		
Abdominal Pain	21 (15.6%)	11 (15.9%)
Anaemia	109 (80.7%)	57 (82.6%)
Dysphagia	8 (5.9%)	2 (2.9%)
Erectile Dysfunction	13 (9.6%)	4 (5.8%)
Fatigue	113 (83.7%)	63 (91.3%)

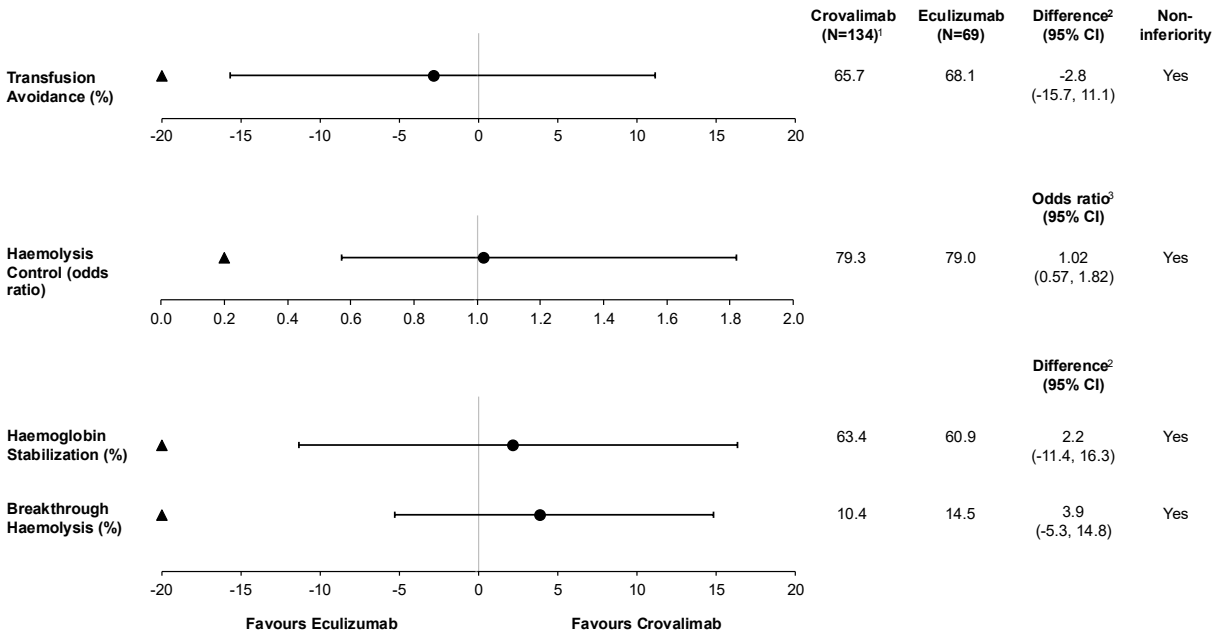
Parameters	Crovalimab (N= 135)	Eculizumab (N= 69)
Haemoglobinuria	79 (58.5%)	45 (65.2%)
MAVE (including Thrombosis)	9 (6.7%)	5 (7.2%)
Shortness of Breath (Dyspnoea)	29 (21.5%)	14 (20.3%)

Note: IQR = interquartile range.
* Two adolescent patients (both 17 years of age) were randomised into the eculizumab arm prior to the opening of the separate descriptive paediatric arm. Both patients switched to crovalimab 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 crovalimab treatment. See below "Paediatric population"
**Includes medicinal products 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 crovalimab compared with eculizumab, based on the non-inferiority (NI) assessment of the following co-primary endpoints: haemolysis control, measured by the mean proportion of patients with LDH ≤ 1.5x ULN from Week 5 to Week 25; and the proportion of patients who achieved transfusion avoidance, defined as patients who are pRBC transfusion-free, from baseline through Week 25. Secondary efficacy endpoints included the proportion of patients with breakthrough haemolysis, proportion of patients with stabilised haemoglobin, and change in fatigue (measured by the FACIT [Functional Assessment of Chronic Illness Therapy]-Fatigue scale) from baseline to Week 25.

Crovalimab was non-inferior compared to eculizumab for both co-primary endpoints of haemolysis control and transfusion avoidance and for the secondary endpoints of haemoglobin stabilisation and breakthrough haemolysis (Figure 1). Figure 2 shows the proportion of patients with LDH ≤ 1.5 ×ULN from baseline through Week 25.

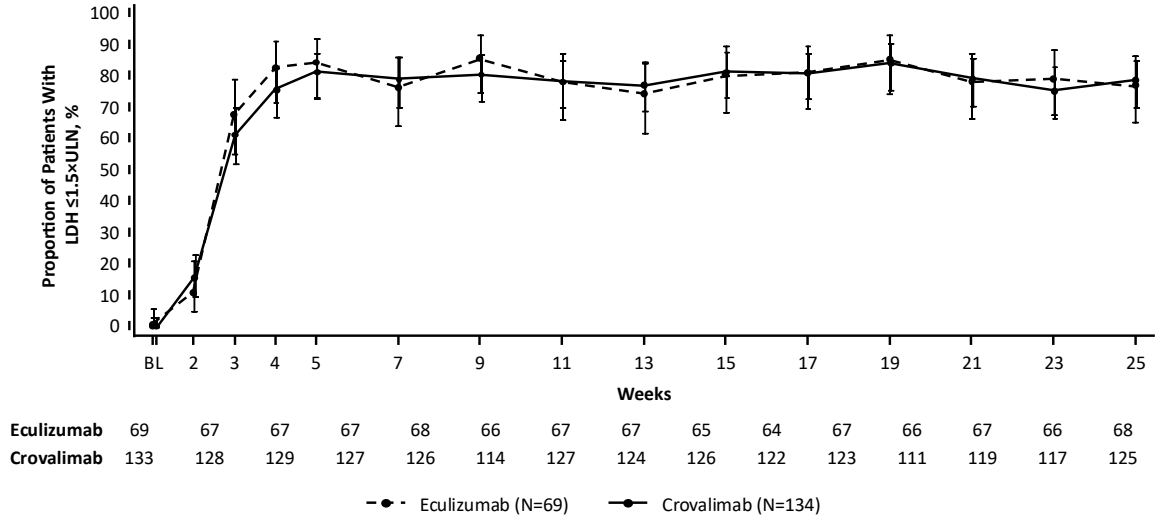
Figure 1: Co-primary and secondary endpoint results in (COMMODORE 2, primary analysis population)



Note: The triangles indicate the non-inferiority margins, and the circles indicate point estimates. CI = confidence interval;

[1] One patient randomised to crovalimab did not have post-baseline LDH and was not included in the primary efficacy analysis.
[2] For Transfusion Avoidance and Haemoglobin Stabilisation, difference is calculated as a weighted difference of crovalimab minus eculizumab. For Breakthrough Haemolysis, difference is calculated as a weighted difference of eculizumab minus crovalimab.
[3] Odds ratio calculated as odds for crovalimab divided by odds for eculizumab

Figure 2: Proportion of patients with LDH ≤ 1.5 × ULN from baseline through Week 25, with 95% CIs (COMMODORE 2, primary analysis population)



Studies in PNH patients previously treated with complement C5 inhibitor therapy

COMMODORE 1 (Study BO42161) - randomised eculizumab switch patients

COMMODORE 1 was a Phase III, randomised, open-label, active-controlled, multicentre clinical study evaluating the safety, pharmacodynamics, pharmacokinetics and exploratory efficacy of crovalimab in patients switching from another complement C5 inhibitor therapy. The primary objective of this study was to evaluate safety (see section 4.8). Eighty-nine patients were randomised 1:1 to receive either crovalimab (n = 45) or eculizumab (n = 44). Patients were eligible to enroll into the randomised arms if they were switching from approved doses of eculizumab and had haemolysis control at screening, defined by LDH level ≤ 1.5 × ULN. Patients were excluded if they had a Major Adverse Vascular Event (MAVE) within the 6 months prior to first study drug administration. Randomisation was stratified by patient transfusion history (whether a patient received a transfusion of pRBCs within 12 months prior to randomisation).

Demographics and baseline characteristics of the randomised study population were balanced between the treatment arms. The median LDH value at baseline was 1.01 x ULN (range: 0.6-1.7) for crovalimab 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 crovalimab arm and 25% in the eculizumab arm, with a mean (SD) of 1.6 (3.7) and 2.3 (5.4) units of transfused pRBC in the crovalimab and eculizumab arms respectively. The baseline median (range) PNH clone sizes for total erythrocytes, monocytes, and granulocytes for crovalimab arm vs eculizumab arms are as follows: 44.6% (2.6 - 100) vs 54.2% (1.3 - 100), 88.6% (13.8 - 100) vs 96.4% (7.6 - 99.9), and 88.1% (5.2 - 100), vs 95.7% (7.9 - 99.9), respectively.

Out of 89 randomised patients, efficacy was evaluated in an exploratory fashion in 76 (n=39 for crovalimab and n=37 for eculizumab) that were enrolled at least 24 weeks before the cut-off date for the primary analysis. Overall, the results of the exploratory efficacy endpoints showed that patients switching to crovalimab from eculizumab maintained disease control. The mean proportion of patients

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

COMMODORE 1 (Study BO42161) and COMMODORE 2 (Study BO42162) - clinically stable switch patients

Supportive data in clinically stable eculizumab switch patients was reported from patients in COMMODORE 1 (25 efficacy evaluable patients) and COMMODORE 2 (29 efficacy evaluable patients) that had been treated with eculizumab for at least 24 weeks in the primary treatment period and had LDH $\leq 1.5 \times$ ULN at switch-to-crovalimab baseline.

Efficacy was evaluated in the patients that had at least 24 weeks of exposure to crovalimab (or otherwise discontinued prior to having reached 24 weeks of treatment). The mean proportion of clinically stable switch patients maintaining haemolysis control from switch baseline through switch Week 25 in COMMODORE 1 and COMMODORE 2 was 98.7% [95% CI: 96.2, 99.5] and 95.3% [95% CI: 89.5, 97.9], respectively. Transfusion avoidance was observed in 80.0% [95% CI: 58.70, 92.39] and 86.2% [95% CI: 67.43, 95.49] of the clinically stable switch patients, respectively. These results in clinically stable eculizumab switch patients were consistent with the results in randomised eculizumab switch patients during the primary treatment period of COMMODORE 1.

Furthermore, in the non-randomised arm of COMMODORE 1, of the 19 clinically stable patients switching from ravulizumab, 95.8% [95%CI: 89.11, 98.43] maintained haemolysis control and 57.9% [95% CI: 33.97, 78.88] patients were transfusion avoidant from baseline to Week 25.

Immunogenicity

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

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medicinal products and underlying disease. For these reasons, comparison of incidence of antibodies to crovalimab 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 crovalimab and 38.2% (26/68) of patients who switched from treatment with another C5 inhibitor to crovalimab. 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 crovalimab, respectively.

Across Phase III 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 (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, out of 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%) ADA positive patients had a loss of pharmacological activity (based on CH50 or free C5) coinciding with a loss of exposure, and loss of efficacy manifested as a sustained loss of haemolysis control in 7 patients (1.8%). There was no evidence for a clinical impact of ADA status on the safety profile of Piasky (see sections 4.4 and 4.8).

Paediatric population

Ten paediatric patients (with body weight ≥ 40 kg) treated with crovalimab in COMMODORE 2 (n = 7; 13 – 17 years old) and COMMODORE 3 (n = 3; 15 – 17 years old) were evaluable for efficacy.

Nine patients were treatment- naive and 1 patient switched from eculizumab to crovalimab in the extension period. All paediatric patients received the same dosing as adult patients based on body weight. All 9 treatment-naive patients achieved haemolysis control (defined as LDH ≤ 1.5 x ULN) by Week 4 and this was maintained in 7 patients at each visit from baseline to Week 25; the patient switching from eculizumab to crovalimab maintained haemolysis control through 24 weeks of treatment in the extension period. Seven out of the 10 paediatric patients achieved transfusion avoidance and haemoglobin stabilisation, and no patients had a breakthrough haemolysis event during the 24-week treatment period.

Overall, the treatment effect of crovalimab in paediatric PNH patients was similar to that observed in adult PNH patients.

5.2 Pharmacokinetic properties

The pharmacokinetics of crovalimab have been characterised both in healthy volunteers and in patients with PNH. The pharmacokinetics were characterised using non-linear mixed effects pharmacokinetic analysis methods, based on a pooled database composed of 9 healthy volunteers and 210 and 211 treatment-naïve patients and patients who switched from previous treatment with another C5 inhibitor to crovalimab, respectively.

The concentration-time course of crovalimab is best described using a two-compartment open model with first-order elimination and a first order subcutaneous absorption constant. 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 crovalimab, an additional time-varying clearance parameter, which decreases exponentially with time, was added. At steady state, exposure is expected to be similar between treatment naïve and switch patients.

Absorption

The absorption rate constant was estimated to be 0.126 day^{-1} [CV%: 38.3]. Following subcutaneous administration, the bioavailability was estimated at 83.0% [CV%: 116].

Distribution

The central volume of distribution was estimated to be 3.23 L [CV%: 22.4] and the peripheral volume of distribution was estimated as 2.32 L [CV%: 70.6].

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

Biotransformation

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

Elimination

The clearance was estimated to be 0.0791 L/day [CV%: 20.6]. The terminal half-life of crovalimab was estimated as 53.1 days [CV%: 39.9], which is longer compared to other humanised IgG antibodies. This long half-life is consistent with the recycling properties of crovalimab.

Special populations

No pharmacokinetic studies with crovalimab have been conducted in special populations. Bodyweight was shown to be a significant covariate, with clearances and volumes of distribution increasing and crovalimab exposure decreasing as bodyweight increases. Therefore, posology of crovalimab is based on the bodyweight of the patient (see section 4.2).

After inclusion of bodyweight in the model, the population pharmacokinetics analyses in patients with PNH showed that age (13 – 85 years) and gender did not meaningfully influence the pharmacokinetics of crovalimab. No further dose adjustment is required.

Race/ethnicity was also shown not to have an impact on the pharmacokinetics of crovalimab; however, data are limited in Black patients and therefore not considered conclusive in this population.

Elderly

No dedicated studies have been conducted to investigate the pharmacokinetics of crovalimab in patients aged ≥ 65 years, however 46 (10.9%) elderly PNH patients were enrolled in clinical studies, including 35 patients aged 65-74 years, 10 patients aged 75-84 years, and 1 patient aged ≥ 85 years. The data obtained in PNH clinical studies indicates that exposure in patients aged ≥ 65 years is comparable to that of younger patients in other age groups, however, due to the limited data in patients ≥ 85 years, the pharmacokinetics of crovalimab in those subjects is unknown.

Renal impairment

No dedicated studies have been conducted to investigate the pharmacokinetics of crovalimab in patients with renal impairment, however the data obtained in PNH clinical studies (62 [14.7%] patients with mild renal impairment, 38 [9%] patients with moderate renal impairment, and 4 [1%] patients with severe renal impairment) indicate that exposure in patients with mild, moderate, or severe renal impairment is comparable to that of patients without renal impairment. However, limited data were obtained for patients with severe renal impairment in PNH clinical studies.

Hepatic impairment

No dedicated studies have been conducted in patients with hepatic impairment, however data obtained in PNH clinical studies indicate that exposure in patients with mild hepatic impairment (46 [11%] as graded based on alanine aminotransferase levels) are comparable to that of patients without hepatic impairment. Limited pharmacokinetic data were available in PNH patients with moderate (0 [0%]) to severe (1[0.23%]) hepatic impairment, therefore the impact of moderate or severe hepatic impairment on the pharmacokinetics of crovalimab is unknown and no dose recommendation can be provided (see section 4.2).

Paediatric population

Data obtained in 12 paediatric patients (13-17 years old) in the PNH clinical studies indicates that exposure in paediatric patients 12 years of age or older with a weight of 40 kg and above was found to be comparable to that of adult patients.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard related to crovalimab treatment for humans based on conventional studies of, repeated dose toxicity (including safety pharmacology endpoints), and toxicity to reproduction and development.

Genotoxicity

No dedicated studies have been performed to establish the genotoxic potential of crovalimab. Monoclonal antibodies are not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

No studies have been performed to establish the carcinogenic potential of crovalimab. Assessment of available evidence related to pharmacodynamic effects and animal toxicology data do not indicate carcinogenic potential of crovalimab.

Reproductive and developmental toxicity

Repeated administration of crovalimab to pregnant cynomolgus monkeys during the gestation period induced no maternal toxicity and did not affect pregnancy outcome. No effects on the viability, growth and development of the infants were observed during the 6-month postnatal period.

Fertility

No effects on female or male reproductive organs were observed in cynomolgus monkeys following repeated administration of crovalimab for up to 6 months. Separate animal fertility studies have not been conducted with crovalimab.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Arginine hydrochloride
L-Histidine
Poloxamer 188
L-Aspartic acid
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

The expiry date of the product is indicated on the packaging materials.

Prior to administration, unopened vials of Piasky may be stored out of the refrigerator at room temperature if needed and then returned to refrigeration. For temperature excursions outside 2 °C – 8 °C, the unopened vial can be kept at room temperature (up to 30 °C) in its outer carton for a cumulative period of no longer than 7 days. Discard if stored out of the refrigerator at room temperature for longer than 7 days.

Diluted solution for intravenous infusion

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the diluted solution for intravenous infusion should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

If the diluted solution is prepared under controlled and validated aseptic conditions, the medicinal product can be stored 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 4.

Table 4: Storage conditions for the solution for infusion prepared using aseptic conditions

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)

Undiluted solution for subcutaneous injection

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless preparation has taken place in controlled and validated aseptic conditions.

If Piasky is transferred from the vial to the syringe under controlled and validated aseptic conditions, the medicinal product in the capped syringe can be stored 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.

6.4 Special precautions for storage

Unopened vial

Store in a refrigerator (2 °C – 8 °C).

Do not freeze. Do not shake.

Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted solution for intravenous infusion and the undiluted solution for subcutaneous injection, see section 6.3.

6.5 Nature and contents of container

Solution for injection/infusion in a 2 mL single-use vial (Type I glass) with a stopper (rubber) and a seal (aluminium).

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

Piasky vial is for single use only.

Piasky is used diluted for intravenous infusion or undiluted for subcutaneous injection.

Piasky should be inspected visually to ensure there is no particulate matter or discolouration prior to administration. Piasky is a sterile clear to strongly opalescent, and almost colourless to brownish-yellow solution. Piasky should be discarded if the medicinal product looks cloudy, discoloured or has particles in it.

Intravenous administration

Piasky must be prepared by a healthcare professional under aseptic technique. Piasky solution must be diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion 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 5) 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 sodium chloride 9 mg/mL (0.9%) solution for infusion 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 5: 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)
1,000	4	5.9	250
1,500	6	8.8	250
1,000	10	5.9	100
1,500	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 particles and discard if present.
4. Flushing of infusion line is required in order to ensure complete administration of the entire dose.

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), or polytetrafluorethylene (PTFE).

For storage conditions of the infusion bags, see section 6.3.

Subcutaneous administration

Piasky should be used undiluted and should be prepared using aseptic technique. 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, 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 1,020 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: Hypodermic needle, stainless steel, sterile, gauge 25 G, 26 G or 27 G, length from 9 to 13 mm, single use, latex free and non-pyrogenic, preferably including safety needle shield.

Please see section 4.2 for additional information on administration.

Any unused 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).

7 MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd., P.O.Box 6391 Hod Hasharon 4524079.

8 MARKETING AUTHORISATION NUMBER(S)

179-25-38166-00

9 MANUFACURER

F. Hoffmann-La Roche Ltd. Basel, Switzerland
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