NOVARTIS

RYVERNA

(Crizanlizumab)

100 mg/ 10 ml Concentrate for solution for infusion

Professional Information

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1. NAME OF THE MEDICINE

RYVERNA 100 mg/ 10 ml Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL vial contains 100 mg of crizanlizumab.

Crizanlizumab is a recombinant humanized IgG2 kappa anti-P-selectin monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells.

Excipients

Sucrose, sodium citrate, citric acid, polysorbate 80, water for injection.

For the full list of excipients, see section 6.1.

Contains sugar : sucrose (753.3 mg per 10ml vial)

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Colorless to slightly brownish-yellow liquid, free from visible particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RYVERNA is indicated for the prevention of vaso-occlusive crises in sickle cell disease patients aged 16 years and over.

4.2 Posology and method of administration

Posology

The recommended dose of RYVERNA is 5 mg/kg administered over a period of 30 minutes by intravenous (IV) infusion at Week 0, Week 2, and every 4 weeks thereafter.

RYVERNA can be given alone or with hydroxyurea (hydroxycarbamide).

Special populations

Hepatic impairment

No studies have been performed in patients with hepatic impairment.

Renal impairment

No studies have been performed in patients with renal impairment.

Elderly (age 65 years and over)

No studies have been performed in patients 65 years of age or above.

Paediatric population

The safety and efficacy of RYVERNA in paediatric patients below the age of 16 years have not been established. RYVERNA is not recommended in this age group.

Method of administration

RYVERNA should be administered by a healthcare professional. RYVERNA should be diluted before administration with either sodium chloride 0.9% or dextrose 5%, and must be dosed on the basis of body weight. RYVERNA diluted solution must be administered through a sterile, non-pyrogenic 0.2 micron in-line filter by intravenous (IV) infusion over a period of 30 minutes. It must not be administered as IV push or bolus.

Instructions for use and handling

RYVERNA 10 mg/mL concentrate for solution for infusion vials are for single use only (see section 4.2 Posology and method of administration).

Each 10 mL vial contains 100 mg crizanlizumab.

How to prepare RYVERNA solution for infusion

The diluted solution for infusion should be prepared by a healthcare professional using aseptic techniques. The total dose and required volume of RYVERNA depends on the patient's body weight; 5 mg of crizanlizumab is administered per kg bodyweight.

The volume of RYVERNA to be used for the preparation of the infusion is calculated

according to the following equation:

Figure 1-1 Volume of RYVERNA needed for a single administration

$$\text{Volume (mL)} = \frac{\text{Patient's body weight (kg) x prescribed dose} \quad [5\ \text{mg/kg}]}{\text{Concentration of \{Tradename\}} \quad [10\ \text{mg/mL}]}$$

1. Obtain the number of vials of RYVERNA required to deliver the prescribed dose and bring them to room temperature (for a maximum of 4 hours). One vial is needed for every 10 mL of RYVERNA (see Table 1-1).

Table 1-1 Number of vials needed by body weight (kg)

Body weight (kg)	Dose (mg)	Volume (mL)	Vials (n)
40	200	20	2
60	300	30	3
80	400	40	4
100	500	50	5
120	600	60	6

2. Visually inspect the vials.

- The solution in the vials should be clear to opalescent. Do not use if particles are present in the solution.
- The solution should be colorless or may have a slight brownish-yellow tint.

3. Withdraw a volume equal to the required volume of RYVERNA from a 100 mL infusion bag containing either sodium chloride 0.9% or dextrose 5% and discard.

- No incompatibilities between the diluted RYVERNA solution and infusion bags composed of polyvinylchloride (PVC), polyethylene (PE) and polypropylene (PP) have been observed.

4. Withdraw the necessary volume of RYVERNA from the vials and inject slowly into the

previously prepared infusion bag.

- The solution must not be mixed or co-administered with other drugs through the same intravenous line.
- Keep the volume of RYVERNA added to the infusion bag in the range of 10 mL to 96 mL.

5. Mix the diluted solution by gently inverting the infusion bag. DO NOT SHAKE.

6. Discard any unused RYVERNA.

Storage of the diluted solution

The diluted solution for infusion should be administered as soon as possible.

If not administered immediately, store the prepared solution either:

- At room temperature up to 25°C for no more than 4.5 hours from the start of the preparation to completion of the infusion.
- Under refrigeration at 2°C to 8°C for no more than 24 hours from the start of the preparation to completion of the infusion. This includes the storage of the diluted solution at 2°C to 8°C and the time to warm up at room temperature.

Administration

RYVERNA diluted solution must be administered through a sterile, non-pyrogenic 0.2 micron in-line filter by intravenous infusion over a period of 30 minutes.

No incompatibilities have been observed between RYVERNA and infusion sets composed of polyvinylchloride (PVC), polyethylene (PE-lined PVC), polyurethane, and in-line filter membranes composed of polyethersulfone (PES), polyamide (PA), polysulphone (PSU).

After administration of RYVERNA, flush the line with at least 25 mL sodium chloride 0.9% or dextrose 5%.

Delayed or missed dose

If a dose is missed, RYVERNA should be administered as soon as possible.

- If RYVERNA is administered within 2 weeks after the missed dose, dosing should be continued according to the patient's original schedule.
- If RYVERNA is administered more than 2 weeks after the missed dose, dosing should be continued every 4 weeks thereafter.

Management recommendations for infusion-related reactions

The table below summarizes recommendations for the management of infusion-related reactions (see 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects)

Severity of Adverse Drug Reaction	**Management recommendation**
Mild to Moderate IRR	Temporarily interrupt the infusion or reduce the infusion rate Initiate symptomatic treatment* (e.g. paracetamol or nonsteroidal anti-inflammatory drug (NSAID) and/or antihistamine) For subsequent infusions consider premedication and/or slower infusion rate
Severe IRR	Discontinue treatment with RYVERNA Institute appropriate therapy*

**Caution should be exercised with corticosteroids in patients with sickle cell disease unless clinically indicated (e.g. treatment of anaphylaxis)*

Special precautions for disposal

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

4.3 Contraindications

Hypersensitivity to RYVERNA or any of the excipients, (see section 6.1).

4.4 Special warnings and precautions for use

Infusion related reactions

In clinical studies, infusion-related reactions (defined as occurring during/within 24 hours) were observed in 3 (2.7%) patients treated with RYVERNA 5 mg/kg (see 4.8 Undesirable effects).

In the post-marketing setting, cases of infusion-related reactions including severe pain events were reported, with the majority occurring during the first and second infusions. Some patients also experienced subsequent complications such as acute chest syndrome and fat embolism, particularly those treated with steroids.

Patients should be monitored for and advised of signs and symptoms of infusion-related reactions which may include pain in various locations, headache, fever, chills, nausea, vomiting, diarrhea, fatigue, dizziness, pruritus, urticaria, sweating, shortness of breath or wheezing.

In the event of a severe infusion-related reaction, RYVERNA should be discontinued and appropriate therapy should be instituted (see section 4 Dosage regimen and administration).

For management recommendations of a mild or moderate infusion-related reaction see 4.2 Dosage regimen and administration.

Caution should be exercised with corticosteroids in patients with sickle cell disease unless clinically indicated (e.g. treatment of anaphylaxis).

Laboratory test interference: automated platelet counts

Interference with automated platelet counts (platelet clumping) has been observed in patients treated with RYVERNA in clinical studies, in particular when tubes containing EDTA (ethylenediaminetetraacetic acid) were used. This may lead to unevaluable or falsely decreased platelet counts. There is no evidence that RYVERNA causes a reduction in circulating platelets or has a pro-aggregant effect in vivo.

To mitigate the potential for laboratory test interference, it is recommended to run the test as soon as possible (within 4 hours of blood collection) or use citrate tubes. When needed, platelet counts can be estimated via a peripheral blood smear.

RYVERNA contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase- isomaltase insufficiency should not use this medicine. RYVERNA contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Interactions between crizanlizumab and other medicinal products have not been investigated in dedicated studies.

Monoclonal antibodies are not metabolized by cytochrome P450 (CYP450) enzymes. Therefore, medicinal products that are substrates, inhibitors or inducers of CYP450 are not expected to affect the pharmacokinetics of crizanlizumab. In clinical studies, hydroxyurea (hydroxycarbamide) had no effect on crizanlizumab pharmacokinetics in patients.

No effect on exposure of co-administered medicinal products is expected based on the metabolic pathways of monoclonal antibodies.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of RYVERNA in pregnancy has not been established.

Crizanlizumab is an IgG antibody that crosses the placental barrier.

As there is no adequate experience in pregnant women, RYVERNA should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

Animal reproduction studies in cynomolgus monkeys have not shown embryo-fetal toxicity or risk of increased fetal abnormalities after intravenous administration of crizanlizumab during organogenesis at doses up to 50 mg/kg (approximately 16 times the human clinical exposure based on AUC in patients with sickle cell disease at 5 mg/kg once every four weeks).

Breastfeeding

A decision must be made whether to discontinue breast-feeding or to discontinue RYVERNA therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Because many medicinal products, including antibodies, can be transferred into human milk, a risk to the newborns/infants cannot be excluded.

Fertility

There are no data on the effect of RYVERNA on human fertility.

In a 26-week repeat-dose toxicity study, cynomolgus monkeys were administered crizanlizumab once every 4 weeks at doses up to 50 mg/kg (at least 13.5 times the human clinical exposure based on

AUC in patients with sickle cell disease at 5 mg/kg once every four weeks). There were no adverse effects of crizanlizumab on male and female

reproductive organs (organ weights, macroscopic and microscopic evaluations), sperm evaluations (motility, counts, morphology) and female menstrual cycles (number and mean duration) suggesting no effect on fertility under crizanlizumab treatment.

4.7 Effects on ability to drive and use machines

RYVERNA may have an influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of RYVERNA has been evaluated in 175 patients with sickle cell disease (any genotype including HbSS, HbSC, Hbbeta0-thalasemia, and Hbbeta+-thalasemia) in two studies: the pivotal study, SUSTAIN, a 52-week, randomized, double-blind, placebocontrolled study (N=66 at 5 mg/kg and N=64 at 2.5 mg/kg), and a single arm, open label pharmacokinetics/pharmacodynamics and safety study (N=45 at 5 mg/kg). Among the 111 patients exposed to the recommended dose (5 mg/kg), the median (min-max) duration of exposure was 54 weeks (4 to 90 weeks). Seventy-five (75) of the 111 patients (68%) were treated in combination with hydroxyurea (hydroxycarbamide). Use of RYVERNA in combination with hydroxyurea (hydroxycarbamide) did not result in any meaningful differences in safety profile.

The most frequently reported adverse drug reactions (≥10% of patients) in the RYVERNA 5 mg/kg group were arthralgia, back pain, nausea, pyrexia and abdominal pain. These adverse drug reactions, along with myalgia, musculoskeletal chest pain, and diarrhoea, may be signs and symptoms of an

infusion related reaction when observed during/within 24 hours of an infusion. The majority of the adverse drug reactions were mild to moderate (grade 1 to 2). Severe events were observed for pyrexia and arthralgia (1 case each [0.9%], both grade 3).

No discontinuations due to adverse drug reactions were reported with RYVERNA 5 mg/kg.

Tabulated list of adverse reactions

Adverse drug reactions from clinical studies (Table 2-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III):

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 2-1 Percentage of patients with adverse drug reactions in clinical studies

Adverse Drug Reactions	**SUSTAIN RYVERNA 5 mg/ kg N = 66 n (%)**	**SUSTAIN Placebo N = 62 N (%)**	**RYVERNA 5 mg/ kg N = 111 n (%)**	**Frequency* category**
Respiratory, thoracic and mediastinal disorders				
Oropharyngeal pain	4 (6.1)	1 (1.6)	5 (4.5)	common
Gastrointestinal disorders				
Nausea	12 (18.2)	7 (11.3)	18 (16.2)	very common
Abdominal pain**	8 (12.1)	3 (4.8)	12 (10.8)	very common
Diarrhoea	7 (10.6)	2 (3.2)	10 (9.0)	common
Vomiting	5 (7.6)	3 (4.8)	7 (6.3)	common

Skin and subcutaneous tissue disorders				
Pruritis**	5 (7.6)	4 (6.5)	8 (7.2)	common
Musculoskeletal and connective tissue disorders				
Back pain	10 (15.2)	7 (11.3)	16 (14.4)	very common
Arthralgia	12 (18.2)	5 (8.1)	19 (17.1)	very common
Musculoskeletal chest pain	5 (7.6)	0 (0.0)	5 (4.5)	common
Myalgia	5 (7.6)	0 (0.0)	6 (5.4)	common
General disorders and administration site conditions				
Pyrexia	7 (10.6)	4 (6.5)	16 (14.4)	very common
Infusion site reaction**	1 (1.5)	1 (1.6)	3 (2.7)	common
Injury, poisoning and procedural complications				
Infusion-related reaction	2 (3.0)	0 (0.0)	3 (2.7)	common

**Frequency from safety pool (SUSTAIN + A2202) at 5 mg/kg*

***The following groupings (in bold) contain the following MedDRA preferred terms*

***Abdominal pain**: abdominal pain, abdominal pain upper,abdominal pain lower, abdominal discomfort and abdominal tenderness **Pruritus**: pruritus and vulvovaginal pruritus*

***Infusion site reaction**: Infusion site extravasation, infusion site pain and infusion site swelling*

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with RYVERNA via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known:

General disorders and administration site conditions
Pain*
* *pain in various locations occurring during/within 24 hours of the infusion (e.g. potential IRR) (see 4.4 Warnings and special precautions)*

Immunogenicity

In clinical studies, treatment-induced anti-crizanlizumab antibodies were detected in 1.9 % of patients who received RYVERNA.

There was no evidence of altered pharmacokinetics or safety profile with anti-crizanlizumabantibody development.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

5. PHARMACOLOGICAL PROPERTIES

5.2 Pharmacokinetic properties

Absorption

Crizanlizumab is administered intravenously. The median time to reach maximum serum concentration of crizanlizumab (Tmax) was 1.63 hours at steady state following an intravenous administration of 5 mg/kg over a period of 30 minutes in sickle cell disease patients.

Distribution

Since crizanlizumab is a humanized monoclonal antibody, its distribution is typical of endogenous human antibodies within the vascular and extracellular spaces. The volume of distribution (Vz) was 4.26 L after a single 5 mg/kg intravenous infusion of crizanlizumab in healthy volunteers.

Biotransformation/ Metabolism

Antibodies are primarily eliminated via proteolysis by lysosomal enzymes in the liver to small peptides and amino acids.

Elimination

In healthy volunteers, the mean terminal elimination half-life (T1/2) was 10.6 days and the mean clearance was 11.7 mL/hr at crizanlizumab dose level 5 mg/kg. In patients with sickle cell disease, the mean elimination T1/2 during dosing interval was 7.6 days. There was no indication of accelerated clearance or time-dependent change in the pharmacokinetic properties of crizanlizumab following repeated administration.

Linearity/ non-linearity

The exposure to crizanlizumab (mean Cmax, AUClast, or AUCinf) increased in non-linear manner over the dose range of 0.2 to 8 mg/kg in healthy volunteers.

Special populations

Renal/hepatic impairment

No dedicated studies have been performed to investigate the pharmacokinetics of crizanlizumab in patients with renal or hepatic impairment.

Pediatric patients below 16 years

Pharmacokinetics in pediatric patients below the age of 16 years have not been investigated.

5.3 Preclinical safety data

Non-clinical data revealed no hazard for humans based on tissue cross-reactivity testing, safety pharmacology and repeated dose studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose 753.3 mg, Sodium citrate 50.53 mg, Citric acid 5.40 mg, Polysorbate 80: 2.00 mg, Water for injection: 10.0 ml.

6.2 Incompatibilities

RYVERNA must not be mixed with other medicinal products.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a refrigerator between 2 °C – 8 °C.

Do not freeze.

Prior to use, the unopened vial may be kept at room temperature (25 °C) for up to 24 hours. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

10 mL colorless glass vial closed with a grey chlorobutyl rubber stopper and capped with an aluminium cap with a yellow flip-off component.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

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