NOVARTIS

PASURTA®

70 mg/mL solution for injection in pre-filled syringe

140 mg/mL solution for injection in pre-filled syringe

Professional Information

Document status: Final

Approval date: 19 December 2023

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SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

Pasurta® 70 mg/mL solution for injection in pre-filled syringe

Pasurta® 140 mg/mL solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pasurta 70 mg/mL: 70 mg erenumab in 1.0 mL (70 mg/mL) solution for injection in pre-filled syringe.

Pasurta 140 mg/mL: 140 mg erenumab in 1.0 mL (140 mg/mL) solution for injection in pre-filled syringe.

Pasurta is produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells.

For the full list of excipients, see section 6.1.

Contains sugar (sucrose) (see section 6.1).

3. PHARMACEUTICAL FORM

Solution for injection, for subcutaneous use.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pasurta is indicated for prophylaxis of migraine in adults.

4.2 Posology and method of administration

Posology

The recommended dose of Pasurta is 70 mg administered once monthly. Some patients may benefit from a dosage of 140 mg administered once monthly.

If a Pasurta dose is missed, administer as soon as possible. Thereafter, Pasurta can be scheduled monthly from the date of the last dose.

Method of administration

Pasurta is administered subcutaneously.
Pasurta is intended for patient self-administration.

Administration should be performed by an individual who has been trained to administer the product.

For detailed instructions on storage, handling and administration, follow the directions provided in the "section 6.6 Special precautions for disposal and other handling".

Important Administration Instructions

- Visually inspect Pasurta for particles and discolouration. Pasurta is a clear to opalescent, colourless to light yellow solution. Do not use if the solution is cloudy or discoloured or contains flakes or particles.
- Administer Pasurta subcutaneously in the abdomen, thigh, or upper arm. If you want to use the same injection site, make sure it is not the same spot you used for a previous injection. Do not inject into areas where the skin is tender, bruised, red, or hard.
- The pre-filled syringe is for single use and designed to deliver the entire contents with no residual content.

- The grey needle cap of the pre-filled syringe contains a dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

4.3 Contraindications

Pasurta is contraindicated in patients with hypersensitivity to erenumab or to any of the excipients (see section 4.4 Special warnings and precautions for use, 4.8 Undesirable effects 4.8).

4.4 Special warnings and precautions for use

Hypersensitivity Reactions

Serious hypersensitivity reactions, including rash, angioedema, and anaphylactoid reactions, have been reported with Pasurta in post marketing experience. These reactions may occur within minutes, although some may occur more than one week after treatment. If a serious or severe hypersensitivity reaction occurs, discontinue administration of Pasurta and initiate appropriate therapy Thereafter, regard Pasurta as being contraindicated for that patient (see 4.3).

Constipation with Serious Complications

Constipation with serious complications has been reported with Pasurta in post-marketing experience. In a majority of cases, the onset was reported after the first dose of Pasurta treatment; however, patients also experienced events later in treatment. Many cases occurred in patients with a history of constipation or concurrent use of medications associated with decreased gastrointestinal motility. In some severe cases, hospitalization was required, including cases where surgery was necessary.

Monitor patients treated with Pasurta for severe constipation and manage as clinically appropriate. Advise patients to seek medical attention if they develop severe constipation.

Special Populations

Paediatrics

The safety and effectiveness of Pasurta has not been studied in paediatric patients and therefore Pasurta is not recommended for use in paediatric patients.

Geriatrics

Clinical studies of Pasurta did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. No dose adjustment is required as the pharmacokinetics of erenumab are not affected by age.

Hepatic Impairment

No clinical studies have been performed in patients with hepatic impairment. Erenumab, as a human monoclonal antibody, is not metabolized by cytochrome P450 enzymes and hepatic clearance is not a major clearance pathway for erenumab.

Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. Population pharmacokinetic analysis of integrated data from the Pasurta clinical trials did not reveal a difference in the pharmacokinetics of erenumab in patients with mild or moderate renal impairment relative to those with normal renal function. Patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2) have not been studied.

Latex-sensitive individuals

The removable cap of the Pasurta pre-filled syringe contains dry natural rubber latex, which may cause allergic reactions in individuals sensitive to latex.

Pasurta contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Pasurta.

4.5 Interaction with other medicines and other forms of interaction

In an open-label, pharmacokinetic medicine interaction study of Pasurta and a combined oral contraceptive in healthy female subjects, erenumab (140 mg subcutaneous [SC], single-dose) did not affect the pharmacokinetics of a combined oral contraceptive containing ethinyl estradiol and norgestimate.

In a randomized, double-blind, placebo-controlled study in healthy volunteers, concomitant administration of erenumab (140 mg intravenous [IV], single-dose) with sumatriptan had no effect on resting blood pressure compared with sumatriptan alone. Pasurta had no effect on the pharmacokinetics of sumatriptan.

Erenumab is not metabolized by cytochrome P450 enzymes and is unlikely to cause marked changes in pro-inflammatory cytokines that may impact cytochrome P450 enzyme expression or activity. As a result, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Interference with Laboratory and Diagnostic Tests

Interference of Pasurta with laboratory and/or diagnostic tests has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safe use during pregnancy has not been established. Therefore, Pasurta is not recommended for use during pregnancy.

In a cynomolgus monkey reproduction study, there were no effects on pregnancy, embryo foetal or post-natal development (up to six months of age) when erenumab was dosed throughout pregnancy at exposure levels 40 or 17-fold higher than those achieved in patients receiving erenumab at the 70 or 140 mg once monthly dosing regimen, respectively based on area under the concentration curve (AUC). Measurable erenumab serum concentrations were observed in the infant monkeys at birth, confirming that erenumab, like other IgG antibodies, crosses the placental barrier.

Animal studies are not always predictive of human response and therefore, it is not known whether Pasurta can cause foetal harm when administered to a pregnant woman.

Lactation

IgG antibodies, such as Pasurta, are excreted in breast milk. Mothers who are breastfeeding their infants should not take Pasurta.

Fertility

No data are available on the effect of Pasurta on human fertility. There were no adverse effects on surrogate markers of fertility (anatomic pathology or histopathology changes in reproductive organs) in sexually mature monkeys at systemic exposures up to 283 or 123 -fold higher than the clinical dose of 70 or 140 mg once monthly, respectively, based on serum AUC. (see section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines:

Pasurta is expected to have no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the Safety Profile

Data from two phase 3 and two phase 2 clinical studies in migraine were pooled to evaluate the safety of Pasurta in comparison to placebo up to 12 weeks after treatment initiation. There were a total of 2656 patients (1613 Pasurta and 1043 placebo) in these studies. Of these, 893 subjects received 70 mg dose of Pasurta, and 507 subjects received 140 mg dose of Pasurta.

The overall safety population including ongoing open-label extension phases with Pasurta includes 2537 patients (2310.3 patient years) who received at least one dose of Pasurta: 2066 patients were exposed for at least 6 months and 1213 patients were exposed for at least 12 months.

Tabulated Summary of Adverse Reactions

Table 1 summarizes all adverse reactions that occurred in Pasurta-treated patients during the 12-week placebo-controlled period of the pooled trials. Most Adverse Drug Reactions (ADR's) were mild or moderate in severity.

Table 1: Adverse Reactions with Pasurta

System Organ Class	Adverse Reaction	Frequency Category	Overall subject incidence at 70 mg	Overall subject incidence at 140 mg

	Preferred Term		**(N = 893) n (%)**	**(N = 507) n (%)**
Gastrointestinal disorders	Constipation	Common	12 (1.3)	16 (3.2)
Skin and subcutaneous tissue disorders	Pruritus[b]	Common	6 (0.7)[b]	9 (1.8)[b]
Musculoskeletal and connective tissue disorders	Muscle spasm	Common (One Grade 3 (0.2 %) event was reported; all others were Grade 1-2.[c])	1 (0.1)	10 (2.0)
General disorders and administration site conditions	Injection site reactions[a]	Common	50 (5.6)[a]	23 (4.5)[a]

Note: Frequency is provided by CIOMS category (e.g., Very Common (≥ 10 %), Common (≥ 1 % and < 10 %), uncommon (≥ 0.1 % and < 1 %), rare (≥ 0.01 % and < 0.1 %), very rare (< 0.01 %)).

[a] Injection site reactions includes multiple preferred terms, such as injection site pain and injection site erythema.

[b] Pruritus includes preferred terms of generalized pruritus, pruritus, and pruritic rash.

[c] Severity grades are based on the Common Terminology Criteria for Adverse Events (CTCAE). Grade 1 Mild; Grade 2 Moderate; Grade 3 Severe or medically significant; Grade 4 Life-threatening consequences; Grade 5 Death.

Description of Selected Adverse Reactions

Injection site reactions

In the integrated 12-week placebo-controlled period of studies, in subjects treated with Pasurta the most frequent injection site reactions were injection site pain, injection site erythema, and injection site pruritus. A majority of injection site reactions were Grade 1 in severity (mild) and of short duration. Injection site pain typically subsided within 1 hour after administration. One subject treated with Pasurta 70 mg SC discontinued due to injection site rash and no subject treated with Pasurta 140 mg SC discontinued due to injection site reactions in the 12-week placebo-controlled period of studies.

Constipation

In the integrated 12-week placebo-controlled period of studies, 28 cases of constipation were reported out of 1400 Pasurta-treated patients. All were mild or moderate severity. A majority of the cases (23) had onset within one month after the first dose; however, some patients also presented with constipation later on in treatment. In most cases (18), constipation resolved within three months. All but one case continued treatment.

Post-Marketing Experience

Immune system disorders

- Hypersensitivity reactions including rash, angioedema and anaphylactoid reactions (see section 4.4 Special warnings and precautions for use).

Gastrointestinal disorders

- Constipation with serious complications [see section 4.4].
- Oral sores (e.g., stomatitis, mouth ulceration, oral mucosal blistering).

Skin and subcutaneous tissue disorders

- Alopecia

- Rash (e.g., rash papular, exfoliative rash, rash erythematous, urticaria, blister)

Immunogenicity

There is potential for immunogenicity. The immunogenicity of Pasurta has been evaluated using an immunoassay for the detection of binding anti-erenumab antibodies. For patients whose sera tested positive in the screening immunoassay, an in vitro biological assay was performed to detect neutralizing antibodies.

In the four migraine prophylaxis efficacy studies [20120178, 20120295, 20120296 and 20120297], the incidence of anti-erenumab antibody development during the double-blind treatment phase was 6.3 % (56/884) among subjects receiving the 70 mg dose of Pasurta (three of whom had in vitro neutralizing activity) and 2.6 % (13/504) among subjects receiving 140 mg dose of Pasurta (none of whom had in vitro neutralizing activity). There was no impact of anti-erenumab antibody development on efficacy or safety of erenumab.

The incidence of anti-drug antibodies (ADAs) is influenced by many factors and is highly dependent on the sensitivity and specificity of the applied assay.

4.9 Overdose

There is no experience with overdose in clinical trials with Pasurta. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, antimigraine preparations ATC code: N02CD01

Mechanism of Action

Erenumab is a human monoclonal antagonist antibody against the CGRP receptor with no significant pharmacological activity at adrenomedullin, calcitonin, and amylin receptors and lacks agonist activity at the CGRP receptor.

CGRP is a neuropeptide that modulates nociceptive signaling and a vasodilator that has been associated with migraine pathophysiology. In contrast with other neuropeptides, CGRP levels have been shown to increase significantly during migraine and return to normal with headache relief. Intravenous infusion of CGRP induces migraine-like headache in patients suggesting that CGRP may play a causal role in migraine.

The CGRP receptor is located at sites that are relevant to migraine pathophysiology. Erenumab potently and specifically competes with the binding of CGRP and inhibits its function at the CGRP receptor.

Pharmacodynamic effects

In a randomized, double-blind, placebo-controlled study (20140254) to evaluate the effect of Pasurta (140 mg IV, single-dose) in patients with stable angina, Pasurta did not decrease exercise duration during a treadmill test compared to placebo and did not aggravate myocardial ischaemia in these patients.

5.2 Pharmacokinetic Properties

Erenumab exhibits non-linear kinetics as a result of binding to CGRP receptor. Subcutaneous administration of a 70 mg and140 mg dose in healthy volunteers resulted in a C_{max} mean (standard deviation [SD]) of 6.1 (2.1) mcg/mL and 15.8 (4.8) mcg/mL respectively, and AUC_{last} mean (SD) of 159 (58) day*mcg/mL and 505 (139) day*mcg/mL respectively.

Less than 2-fold accumulation was observed in trough serum concentrations (C_{min} [SD] 5.7 [3.1] and 6.2 [2.9] mcg/mL for episodic and chronic migraine subjects, respectively following 70 mg doses; C_{min} [SD] 12.8 [6.53] and 14.9 [6.45] mcg/mL for episodic and chronic migraine subjects, respectively following 140 mg doses) administered subcutaneously every 4 weeks and serum trough concentrations approached steady state by 12 weeks of dosing. The effective half-life of Pasurta is 28 days.

Absorption

Following a single subcutaneous dose of 70 mg or 140 mg Pasurta administered to healthy adults, median peak serum concentrations were attained in approximately 6 days, and estimated absolute bioavailability was 82 %.

Distribution

Following a single 140 mg intravenous dose, the mean (SD) volume of distribution during the terminal phase (Vz) was estimated to be 3.86 (0.77) l.

Metabolism and Excretion

Two elimination phases were observed for Pasurta. At low concentrations, the elimination is predominantly through saturable binding to target (CGRP-R), while at higher concentrations the elimination of Pasurta is largely through a non-specific, non-saturable proteolytic pathway.

Specific Populations

The pharmacokinetics of erenumab were not affected by age, gender, race, migraine subtype (episodic or chronic migraine), or creatinine clearance, across all approved populations based on population pharmacokinetics (PK) analysis.

5.3 Preclinical Safety Data/Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with Pasurta. Pasurta is not pharmacologically active in rodents and has biologic activity in the cynomolgus monkeys, but this species is not an appropriate model for evaluation of tumorigenic risk. The mutagenic potential of Pasurta has not been evaluated; however, monoclonal antibodies are not expected to alter DNA or chromosomes.

There were no adverse effects on surrogate markers of fertility (anatomic pathology or histopathology changes in reproductive organs) in the chronic toxicology study in sexually mature monkeys subcutaneously administered Pasurta at dose levels up to 150 mg/kg twice weekly for 6 months, at systemic exposures up to 283 or 123-fold higher than the clinical dose of 70 mg or 140 mg once monthly, respectively, based on serum AUC.

Animal Toxicology

There were no adverse effects in monkeys dosed up to 150 mg/kg SC twice weekly for up to 6 months at systemic exposures up to 283 or 123-fold higher than the clinical dose of 70 or 140 mg once monthly, respectively, based on serum AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

70 mg per mL pre-filled syringe

- Sucrose: 73 mg/7.3 % (w/v); NF, Ph. Eur., JP
- Glacial acetic acid: 1.5 mg/25 mM; USP, Ph. Eur., JP
- Polysorbate 80: 0.10 mg/0.010 % (w/v); NF, Ph. Eur., JP
- Water for injection
- Sodium hydroxide to pH of 5.2; NF, Ph. Eur., JP

140 mg per mL pre-filled syringe

- Sucrose: 65 mg/6.5 % (w/v); NF, Ph. Eur., JP
- Glacial acetic acid: 2.0 mg/34 mM; USP, Ph. Eur., JP
- Polysorbate 80: 0.10 mg/0.010 % (w/v); NF, Ph. Eur., JP
- Water for injection
- Sodium hydroxide to pH of 5.2; NF, Ph. Eur., JP

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

36 months at 2 °C to 8 °C

6.4 Special precautions for storage

- Store refrigerated at 2 °C to 8 °C in the original carton to protect from light until time of use.
- If removed from the refrigerator, Pasurta should be kept at controlled room temperature (up to 25 °C) in the original carton and must be used within 7 days. Throw away Pasurta that has been left at room temperature for more than 7 days.
- Do not freeze.
- Do not shake.

6.5 Nature and contents of container

- Sterile, preservative-free solution, clear to opalescent; colourless to yellowish solution, practically free from particles.
- The needle shield within the grey needle cap of the pre-filled syringe containing dry natural rubber (a derivative of latex).

Pasurta is provided as:

- Carton of one or two 70 mg/mL or one 140 mg/mL (injection) pre-filled syringe with Type 1 glass syringe and stainless steel needle.

6.6 Special precautions for disposal and other handling

- Prior to subcutaneous administration, allow Pasurta to sit at room temperature for at least 30 minutes and protect from direct sunlight. Do not warm by using a heat source such as hot water or microwave.

- Do not shake the product.
- Visually inspect the solution for particles and discolouration. Do not use if the solution is cloudy, discoloured or contains flakes or particles.
- Doses may be administered in the upper arm, thigh, or abdomen. Injection sites should be rotated, and injections should not be given into areas where the skin is tender, bruised, red, or hard.
- Any unused product or waste material should be disposed of in accordance with local requirements.
- Comprehensive instructions for the administration of Pasurta are provided in the Instructions for Use.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis SA (Pty) Ltd

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg, 2090

South Africa

8. REGISTRATION NUMBER(S)

Pasurta 70 mg/mL solution for injection in a pre-filled syringe: 54/7.3/0587

Pasurta 140 mg/mL solution for injection in a pre-filled syringe: 54/7.3/0588

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 November 2020

10. DATE OF REVISION OF THE TEXT

19 December 2023

(2022-PSB/GLC-1272-s)

11. DOSIMETRY (IF APPLICABLE)

Not applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not applicable