NOVARTIS

Regulatory Affairs

PASURTA®

(erenumab)

70 mg/mL Solution for injection in a prefilled syringe

140 mg/mL Solution for injection in a prefilled syringe

Summary of Product Characteristics (SmPC)

PASURTA®

Anti-Calcitonin Gene-Related Peptide Receptor (anti-CGRPR) monoclonal antibody

ATC code: N02CD01

DESCRIPTION AND COMPOSITION

Pharmaceutical forms

70 mg erenumab in 1.0 mL (70 mg/mL) solution

- 70 mg/mL solution for injection in a pre-filled syringe, subcutaneous use.

140 mg erenumab in 1.0 mL (140 mg/mL) solution.

- 140 mg/mL solution for injection in a pre-filled syringe, subcutaneous use.

Not all dosage forms may be available in all countries.

Active substance

Erenumab.

Excipients

Sucrose, Glacial acetic acid, Polysorbate 80, Water for injection, Sodium hydroxide.

INDICATIONS

Pasurta is indicated for prophylaxis of migraine in adults.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage

The recommended dose of Pasurta is 70 mg administered once monthly.

Some patients may benefit from a dosage of 140 mg administered once monthly [see section CLINICAL STUDIES]

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

Special populations

Pediatrics

The safety and effectiveness of Pasurta has not been studied in pediatric 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.

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.

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.

Effects on ability to drive and use machines

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

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. To administer the 140 mg dose, give two consecutive subcutaneous injection of 70 mg each of Pasurta or one subcutaneous injection of 140 mg.

For detailed instructions on storage, handling and administration, follow the directions provided in the “Instructions for Use”.

Important administration instructions

Visually inspect Pasurta for particles and discoloration. Pasurta is a clear to opalescent, colorless to light yellow solution. Do not use if the solution is cloudy or discolored 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.

Prefilled syringes are for single use and designed to deliver the entire contents with no residual content .

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

CONTRAINDICATIONS

Pasurta is contraindicated in patients with serious hypersensitivity to erenumab or to any of the excipients [see section WARNINGS AND PRECAUTIONS, ADVERSE DRUG REACTIONS].

WARNINGS AND PRECAUTIONS

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 [see section CONTRAINDICATIONS].

ADVERSE DRUG REACTIONS

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 drug 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 of the Adverse Drug Reactions (ADR's) were mild or moderate in severity.

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%)).

Table 1 Adverse drug reactions with Pasurta

System Organ Class	Adverse Drug Reaction Preferred Term	Frequency Category	Overall subject incidence at 70 mg (N = 893) n (%)	Overall subject incidence at 140 mg (N=507) n (%)
General disorders and administration site condition	Injection site reactions[a]	Common	50 (5.6) [a]	23 (4.5)[a]
Gastrointestinal disorders	Constipation	Common	12 (1.3)	16 (3.2)
Musculoskeletal and connective tissue disorders	Muscle spasm	Common	1 (0.1)	10 (2.0)
Skin and subcutaneous tissue disorders	Pruritus[b]	Common	6 (0.7) [b]	9 (1.8)[b]

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

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

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 transient. 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 WARNINGS AND PRECAUTIONS]

Gastrointestinal disorders

- Constipation with serious complications has been reported. In a majority of these cases, the onset was reported after the first dose of Pasurta; however patients have also experienced these events later on in the treatment. Many of the cases of constipation with serious complications were reported for patients who have a history of constipation or concurrently use medications associated with decreased gastrointestinal motility. In some severe cases hospitalization was required.
- 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

As with all therapeutic proteins, 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 highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to erenumab with the incidence of antibodies to other products may be misleading.

INTERACTIONS

In an open-label, pharmacokinetic drug 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.

PREGNANCY, LACTATION, FERTILITY

Pregnancy

There are no adequate and well controlled studies on the use of Pasurta in pregnant women. In a cynomolgus monkey reproduction study, there were no effects on pregnancy, embryo-fetal 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 fetal harm when administered to a pregnant woman. Pasurta should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

It is not known whether Pasurta is present in human milk. There are no data on the effects of Pasurta on the breastfed child or the effects of Pasurta on milk production. Because drugs are excreted in human milk and because of the potential for adverse effects in nursing infants from Pasurta, a decision should be made whether to discontinue nursing or discontinue Pasurta, taking into account the potential benefit of Pasurta to the mother and the potential benefit of breast feeding to the infant.

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 NON-CLINICAL SAFETY DATA).

OVERDOSAGE

There is no experience with overdose in clinical trials with Pasurta. Doses up to 280 mg SC have been administered in clinical trials with no evidence of dose limiting toxicity.

In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required.

CLINICAL PHARMACOLOGY

Mechanism of action

Erenumab is a human monoclonal antagonist antibody against the CGRP receptor with no significant pharmacological activity at adrenomedulin, 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 effect

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 ischemia in these patients.

Pharmacokinetic properties

Erenumab exhibits non-linear kinetics as a result of binding to CGRP receptor. Subcutaneous administration of a 70 mg and 140 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 (V_z) 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 predominately 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.

CLINICAL STUDIES

Pasurta was evaluated for prophylaxis of migraine in two pivotal studies across the spectrum of episodic and chronic migraine. Studies enrolled patients with a history of migraine, with or without aura according to the International Classification of Headache Disorders (ICHD-III) diagnostic criteria.

Pasurta treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for key efficacy outcomes.

Chronic Migraine

Study 1 (Study 20120295)

Pasurta was evaluated for prophylaxis of chronic migraine in a randomized, multi-center, 12 week, placebo-controlled, double-blind study. A total of 667 patients with a history of migraine with or without aura (≥15 headache days per month with ≥8 migraine days per month) were randomized to receive placebo (n = 286), Pasurta 70 mg (n = 191) or Pasurta 140 mg (n = 190) subcutaneous injections monthly for 12 weeks.

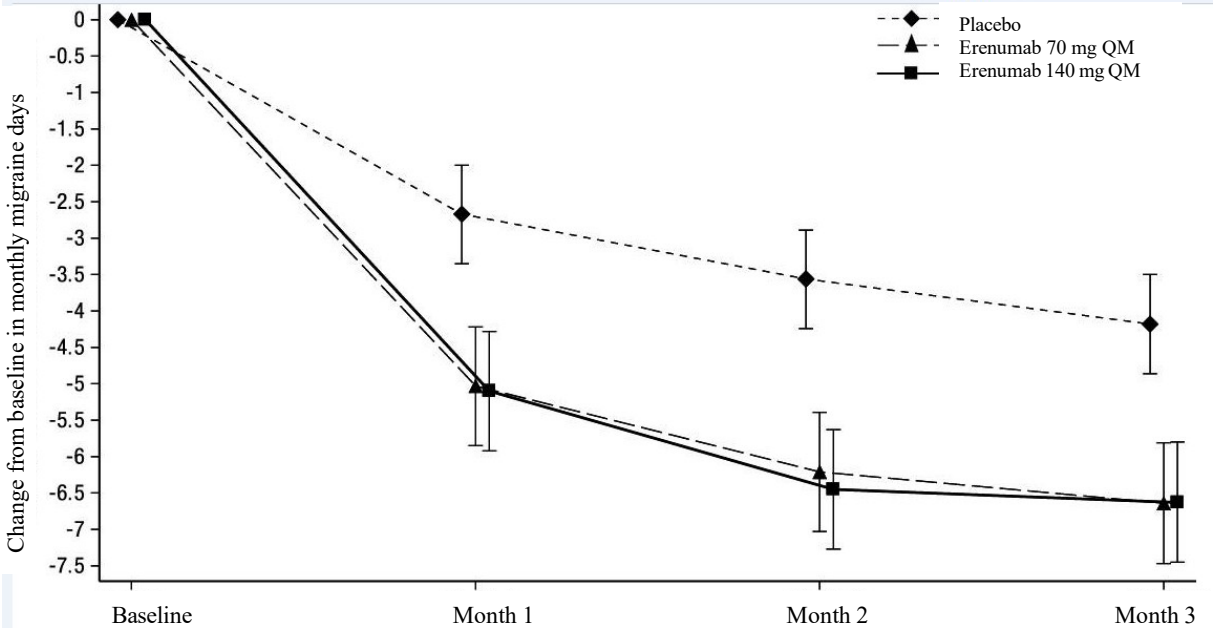
Randomization was stratified by region (North America versus other) and the presence of acute medication overuse (present in 41% of overall patients) excluding patients with opioid overuse. The mean migraine frequency at baseline was approximately 18 migraine days per month and was similar across treatment groups. Patients were allowed to use acute headache treatments including triptans, ergotamine derivatives and NSAIDs during the study.

Patients had a median age of 43 years (range: 18 to 66 years), 83% were female and 94% were white. Patients could have failed (i.e., no therapeutic response) up to three previous prophylactic treatment categories due to lack of efficacy, while there was no limit to the number of previous failures for poor tolerability. Overall in this study population, 68% had failed one or more previous prophylactic treatments due to lack of efficacy or poor tolerability, and 49% had failed two or more previous prophylactic treatments due to lack of efficacy or poor tolerability. In addition to excluding patients with opioid overuse, the study excluded patients with concurrent use of migraine prophylactic treatments. A total of 182 (96%) patients in the Pasurta 140 mg arm, 184 (96%) patients in the Pasurta 70 mg arm, and 265 (93%) patients in the placebo arm completed the study (i.e. completed Week 12 assessment). Of the 23 (3.4%) patients who discontinued treatment, 2 patients in the Pasurta 140 mg-treated group, no patients in the Pasurta 70 mg- treated group, and 2 patients in the placebo group discontinued due to adverse events.

The primary outcome measure was the change from baseline at Month 3 in monthly migraine days. Secondary outcome measures included the achievement of 50 to 100% reduction in monthly migraine days from baseline (≥50% responders), change from baseline in monthly acute migraine specific medication days, and change from baseline in cumulative monthly headache hours. Other than for cumulative monthly headache hours, Pasurta treatment demonstrated statistically significant and clinically meaningful improvements from baseline at Month 3 compared to placebo for efficacy outcomes as summarized in Figure 1 and Table 2.

Reduction in mean monthly migraine days from placebo were observed in a monthly analysis from Month 1 and in a follow up weekly analysis an onset of Pasurta effect was seen from the first week of administration.

Figure 1: Change from baseline in monthly migraine days in Study 1[a]



[a] Least-square means and 95% confidence intervals are presented.
The p-value for the difference in least-square means between erenumab and placebo assessed at Month 3 (primary outcome measure) were all< 0.001 for both Pasurta dose groups.

Table 2 Efficacy Outcomes in Study 1 at Month 3

	Pasurta 70 mg (n = 188)	**Pasurta 140 mg (n = 187)**	**Placebo (n = 281)**	**Treatment difference /Odds ratio**	**p-value[a]**
Efficacy outcomes					
Monthly migraine days (MMD)					
Mean change[b] 95% CI	-6.64 (-7.47; -5.81)	-6.63 (-7.45; -5.80)	-4.18 (-4.86; -3.50)	70 mg:-2.46 (-3.52; -1.39) 140 mg: -2.45 (-3.51; -1.38)	Both <0.001
≥50% MMD responders					
Percentage [%]	39.9%	41.2%	23.5%		
Odds ratio[c] 95% CI				70 mg: 2.18 (1.46, 3.27) 140 mg: 2.34 (1.56, 3.51)	Both < 0.001
≥ 75% MMD responders[d]					
%	17.0	20.9	7.8		n/a
Odds ratio 95% CI				70 mg: 2.43 (1.36; 4.33) 140 mg: 3.13 (1.78; 5.48)	
Monthly acute migraine specific medication days[e]					
Mean change[b] 95% CI	-3.45 (-4.02; -2.87)	-4.13 (-4.70; -3.56)	-1.58 (-2.05; -1.11)	70 mg: -1.86 (-2.60; -1.13) 140 mg: -2.55 (-3.28; -1.82)	Both <0.001
Cumulative headache hours					

Mean change[b] 95% CI	-64.76 (-78.34; -51.17)	-74.53 (-88.05; -61.01)	-55.22 (-66.38; -44.06)	70 mg: -9.54 (-26.98; 7.90) 140 mg: -19.31 (-36.71; -1.92)	ns
Patient-reported outcome measures					
HIT-6					
Mean change[f] 95% CI	-5.6 (-6.5; -4.6)	-5.6 (-6.5; -4.6)	-3.1 (-3.9; -2.3)	70 mg: -2.5 (-3.7, -1.2) 140 mg: -2.5(-3.7, -1.2)	n/a
MIDAS total					
Mean change[f] 95% CI	-19.41 (-25.19; -13.62)	-19.76 (-25.56; -13.97)	-7.54 (-12.40; -2.69)	70 mg: -11.86 (-19.34; -4.39) 140 mg: -12.22 (-19.64; -4.75)	n/a

CI = confidence interval; HIT = headache impact test; MIDAS = migraine disability assessment; MMD = monthly migraine days; ns = not significant; n/a = not applicable

[a] All p-values are reported as unadjusted p-values and are statistically significant after adjustment for multiple comparisons.

[b] Least-square mean (LSM) change from baseline at Month 3, treatment difference and p-value are based on a linear mixed effects model including treatment group, baseline monthly value, stratification factors (region [North America versus Europe] and medication overuse [presence versus absence]), scheduled visit and the interaction of treatment group with scheduled visit, without any imputation for missing data.

[c] Odds ratio and p-value for ≥ 50% responders at month 3 are based on a stratified Cochran-Mantel-Haenszel test after missing data were imputed as non-response.

[d] Post-hoc analysis; no hypothesis testing was performed.

[e] Migraine-specific medications include triptans and ergotamine derivatives.

[f] Change and reduction from baseline were evaluated at the last 4 weeks of the 12-week double-blind treatment phase.

Based on a pre-specified analysis, Pasurta 70 mg and 140 mg were efficacious in patients who had previously been treated with migraine prophylactics. Table 3 provides subgroup results of Study 1 based on prior prophylactic failure(s) due to lack of efficacy or intolerance, in a pre-specified analysis.

Table 3 Efficacy Outcomes in Study 1 at Month 3 in Subgroups Based on Prior Prophylactic Failure

	Pasurta 70 mg (patients never failed/failed ≥1 medication/ failed ≥2 medications, n=64/124/90)	**Pasurta 140 mg (patients never failed/failed ≥1 medication/ failed ≥2 medications, n=62/125/92)**	**Placebo (patients never failed/failed ≥1 medication/failed ≥2 medications, n=84/197/141))**	**Treatment difference / Odds ratio (95% CI)**
Monthly migraine days (MMD)[a] - Mean change[b] (95% CI)				TD
Never failed	-7.86 (-9.33; -6.39)	-6.14 (-7.61; -4.66)	-5.67 (-6.98; -4.36)	70 mg: -2.19 (-4.10; -0.28) 140 mg:-0.47 (-2.39;1.46)
Failed ≥1 medication	-5.98 (-6.99; -4.97)	-6.84 (-7.84; -5.85)	-3.51 (-4.33; -2.70)	70 mg: -2.47 (-3.76; -1.18)

				140 mg:-3.33 (-4.61; -2.06)
Failed ≥2 medications	-5.38 (-6.56; -4.20)	-6.96 (-8.10; -5.82)	-2.68 (-3.63; -1.72)	70 mg: -2.71 (-4.20; -1.21) 140 mg: -4.28 (-5.75; -2.80)
≥50% MMD responders[c]-%				OR[d]
Never failed	50%	41.9 %	38.1 %	70 mg: 1.75 (0.89; 3.43) 140 mg:1.33 (0.67; 2.66)
Failed ≥1 medication	34.7%	40.8 %	17.3 %	70 mg: 2.64 (1.56; 4.48) 140 mg: 3.30 (1.98; 5.51)
Failed ≥2 medications	35.6%	41.3 %	14.2 %	70 mg: 3.46 (1.81; 6.61) 140 mg: 4.18 (2.21; 7.91)
Monthly acute migraine-specific medication days[e] - Mean change[b] (95% CI)				TD
Never failed	-2.48 (-3.31; -1.64)	-2.48 (-3.31; -1.64)	-1.78 (-2.52; -1.05)	70 mg: -0.69 (-1.77; 0.38) 140 mg: -0.69 (-1.78; 0.39)
Failed ≥1 medication	-3.83 (-4.58; -3.08)	-4.90 (-5.64; -4.16)	-1.47 (-2.07; -0.87)	70 mg: -2.36 (-3.31; -1.41) 140 mg: -3.43 (-4.37; -2.49)
Failed ≥2 medications	-4.05 (-4.96; -3.15)	-5.39 (-6.27; -4.51)	-1.26 (-2.00; -0.53)	70 mg: -2.79 (-3.94; -1.65) 140 mg: -4.13 (-5.26; -3.00)

CI = confidence interval; MMD = monthly migraine days; TD = treatment difference; OR = odds ratio

[a] MMD at baseline was approximately 18 migraine days per month and similar across the above subgroups.

[b] Least-square mean (LSM) change from baseline at Month 3 and treatment difference are based on a linear mixed effects model including treatment group, baseline monthly value, stratification factors (region [North America versus other and medication overuse [presence versus absence]), scheduled visit and the interaction of treatment group with scheduled visit, without any imputation for missing data.

[c] Responders are defined as patients who achieve ≥50% reduction on MMD from baseline

[d] Odds ratio for ≥50% responders at Month 3 based on a stratified Cochran-Mantel-Haenszel test after missing data were imputed as non-response.

[e] Migraine-specific medications include triptans and ergotamine derivatives.

In patients with medication overuse (41% of the total population in Study 1), efficacy was observed with 70 mg and 140 mg Pasurta compared to placebo for monthly migraine days [LSM (95% Cl) 70 mg: −3.10 days (−4.83, −1.37)]; 140 mg: -3.10 days (-4.81, -1.39) 50% responders: 34.6% for 140 mg, 36.4% for 70 mg versus 17.7% for placebo), with odds ratio (95% CI) 70 mg: 2.67 (1.36, 5.22);140 mg: 2.51 (1.28, 4.94)) and in acute migraine-specific medication days (LSM (95% CI) 70 mg: -3.33 (-4.72, -1.94); 140 mg: -2.79 (-4.16, -1.42)).

Improvement in functional ability was assessed by the Headache Impact Test (HIT-6) and the Migraine Disability Assessment (MIDAS) questionnaires. Mean change from baseline to Month 3 compared to placebo for the patient reported outcome measures are summarized in Table 2. The established between-group Minimally Important Difference (MID) for the reduction in HIT-6 total score is 2.3.

Episodic Migraine

Study 2 (Study 20120296, STRIVE)

Study 2 was a randomized, multi-center, 24-week, placebo-controlled, double- blind study evaluating Pasurta for prophylaxis of episodic migraine. A total of 955 patients with history of migraine with or without aura for a duration of ≥ 12 months and 4-14 migraine days per month were randomized to receive either Pasurta 70 mg (n=317), Pasurta 140 mg (n = 319), or placebo

(n = 319) by subcutaneous injection monthly for 6 months. Randomization was stratified by use of prophylactic medications (concomitant, prior use or no prior use) and region (North America vs. other). The mean migraine frequency at baseline was approximately 8 migraine days per month and was similar across treatment groups. Patients were allowed to use acute headache treatments including triptans, ergotamine derivatives and NSAIDs during the study.Patients had a median age of 42 years (range: 18 to 65 years), 85% were female and 89% were white. Patients could have failed to respond up to two previous prophylactic treatments. The study excluded patients with medication overuse. Overall, 865 (90.6%) patients completed the double-blind phase, including 287 (90.5%) in the 70 mg group, 294 (92.2%) in the 140 mg group, and 284 (89.0%) in the placebo group. Of the 87 (9.1%) patients who discontinued treatment, 7 patients in the 70 mg Pasurta group, 6 patients in the 140 mg Pasurta group, and 7 patients in the placebo group discontinued due to adverse events.

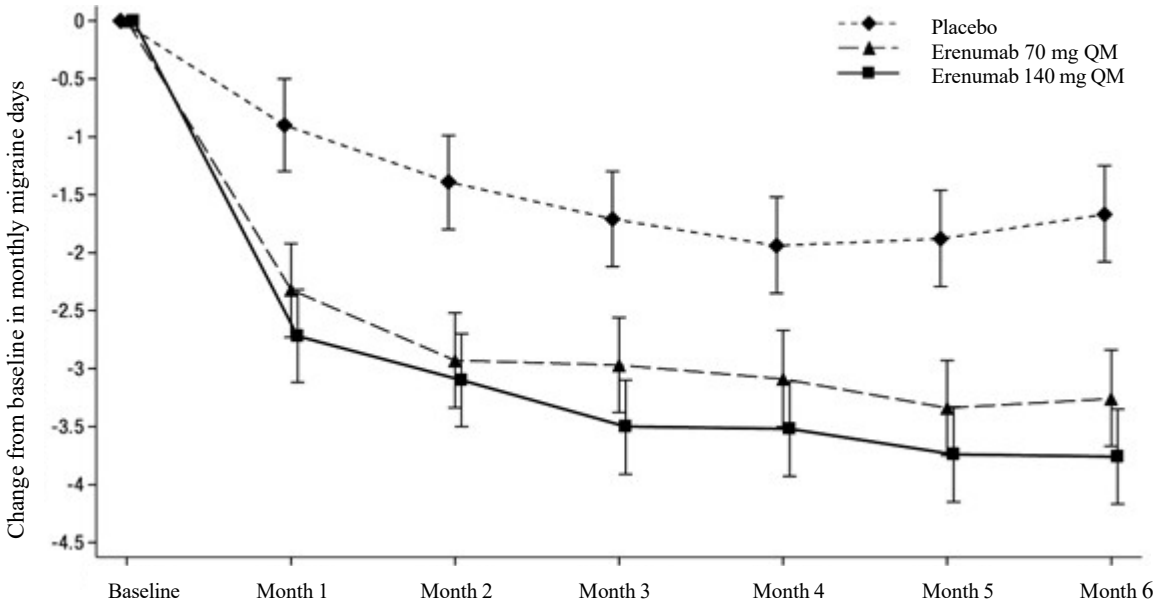
The primary outcome measure was the change from baseline during months 4-6 in monthly migraine days. Secondary outcome measures included the achievement of a 50 to 100% reduction in mean monthly migraine days from baseline (≥50% responders), change from baseline in mean monthly acute migraine specific medication days and change from baseline in the two Migraine Physical Function Impact Diary (MPFID) domain scores: physical impairment (PI) and impact on everyday activities (EA).

The MPFID is a patient reported outcomes instrument that measures the impact of migraine on physical functioning. It contains 13 items evaluating the impact of migraine during the previous 24 hours on two physical functioning concepts of interest – "impact on everyday activities (EA)" (7 items, e.g. difficulty doing activities requiring concentration), "physical impairment (PI)" (5 items, e.g. difficulty doing activities requiring physical effort) and one global item assessing the overall impact on everyday activities. Patients rate the duration of impact or level of difficulty associated with migraine on a daily basis. Monthly MPFID scores are averaged over days with and without migraine; higher scores indicate worse impact on the EA and PI domains.

Pasurta treatment demonstrated statistically significant and clinically meaningful improvements from baseline during Months 4 to 6 compared to placebo for efficacy outcomes as summarized in Figure 2 and Table 4. Differences from placebo were observed as early as Month 1.

Based on a pre-specified analysis, Pasurta 70 mg and 140 mg were efficacious in patients who had previously been treated with migraine prophylactics. Table 5 provides subgroup results of Study 2 based on prior prophylactic failure due to lack of efficacy or intolerance, in a pre-specified analysis.

Figure 2: Change from baseline in monthly migraine days over time in Study 2[a]



[a] Least-square means and 95% confidence intervals are presented.
The p-value for the difference in least-square means between erenumab and placebo assessed as the average over months 4, 5 and 6(primary outcome measure) was < 0.001 for both Pasurta dose groups.

Table 4: Efficacy Outcomes at Months 4-6 in Study 2

	Pasurta 70 mg (n = 312)	**Pasurta140 mg** (n = 318)	**Placebo** (n = 316)	**Treatment difference / Odds ratio**	**p-value[a]**
Efficacy outcomes					
Monthly migraine days (MMD)					
Mean change[b] 95% CI	-3.23 (-3.58; -2.88)	-3.67 (-4.02; -3.33)	-1.83 (-2.18; -1.48)	70 mg: -1.40 (-1.88; -0.92) 140 mg: -1.85 (-2.33; -1.37)	Both <0.001
≥50% MMD responders					
Percentage [%]	43.3 %	50.0%	26.6%		
Odds ratio[c] 95% CI				70 mg: 2.13 (1.52; 2.98) 140 mg: 2.81 (2.01; 3.94)	Both < 0.001
≥ 75% MMD responders[d]					
%	20.8%	22.0 %	7.9 %		n/a
Odds ratio 95% CI				70 mg: 3.14 (1.91, 5.18) 140 mg: 3.35 (2.05, 5.49)	
Monthly acute migraine-specific medication days[e]					
Mean change[b] 95% CI	-1.13 (-1.34; -0.92)	-1.61 (-1.83; -1.40)	-0.20 (-0.41; 0.02)	70 mg: -0.94 (-1.23; -0.64) 140 mg: -1.42 (-1.71; -1.12)	Both <0.001
Patient-reported outcome measures					
MPFID physical impairment domain					

Mean change[b] 95% CI	-4.24 (-5.02; -3.45)	-4.81 (-5.59; -4.03)	-2.38 (-3.16; -1.59)	70 mg: -1.86 (-2.95; -0.77) 140 mg: -2.43 (-3.51; -1.35)	Both <0.001
MPFID impact on everyday activities domain					
Mean change[b] 95% CI	-5.52 (-6.28; -4.75)	-5.86 (-6.62; -5.10)	-3.30 (-4.06; -2.53)	70 mg: -2.22 (-3.28; -1.16) 140 mg: -2.57 (-3.62; -1.51)	Both <0.001
HIT-6					
Mean change 95% CI	-6.7 (-7.4; -6.0)	-6.9 (-7.6; -6.3)	-4.6 (-5.3; -4.0)	70 mg: -2.1 (-3.0; -1.1) 140 mg: -2.3 (-3.2; -1.3)	n/a
MIDAS (modified) total					
Mean change 95% CI	-6.7 (-7.6; -5.9)	-7.5 (-8.3; -6.6)	-4.6 (-5.5; -3.8)	70 mg: -2.1 (-3.3, -0.9) 140 mg: -2.8 (-4.0; -1.7)	n/a
Response on MPFID-physical impairment domain					
Percentage (%)[f]	39.1	42.5	30.1		
Odds Ratio 95% CI				70 mg: 1.49 (1.07; 2.08) 140 mg: 1.73 (1.24; 2.40)	
Response on MPFID-impact on everyday activities domain					
Percentage (%)[f]	49.0	50.3	34.5		
Odds Ratio 95% CI				70 mg: 1.83 (1.33; 2.52) 140 mg: 1.93 (1.40; 2.67)	

CI = confidence interval; HIT = headache impact test; MIDAS = migraine disability assessment; n/a = not applicable; MMD = monthly migraine days; MPFID = Migraine Physical Function Impact Diary; ns = not significant

[a] All p-values are reported as unadjusted p-values and are statistically significant after adjustment for multiple comparisons

[b] Least-square mean change from baseline at Months 4 to 6, treatment difference and p-value are based on a linear mixed effects model including treatment group, baseline value, stratification factors (region [North America vs rest of world] and prior prophylactic medication use [naïve, prior use only, concurrent use]), scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data.

[c] Odds ratio and p-value for ≥ 50% responders at month 4-6 are based on a stratified Cochran-Mantel-Haenszel test after missing data were imputed as non-response.

[d] Post-hoc analysis; no hypothesis testing was performed..

[e] Migraine-specific medications include triptans and ergotamine derivatives.

[f] reduction from baseline in PI, EA average monthly domain score >=5

Table 5: Efficacy Outcomes at Months 4 to 6 in subgroups based on prior prophylactic failure in Study 2

	Pasurta 70 mg (patients	**Pasurta 140 mg (patients**	**Placebo (patients never failed/failed ≥1**	**Treatment difference (TD) / Odds ratio (OR) (95% CI)**

	never failed/failed ≥1 medication, n=185/127)	**never failed/failed ≥1 medication, n=202/116)**	**medication, n=190/126)**	
Monthly migraine days (MMD) [a] - Mean change[b] (95% CI)				TD
Never failed	-3.26 (-3.83, -2.70)	-3.63 (-4.15; -3.10)	-2.32 (-2.87; -1.78)	70 mg: -0.94 (-1.54, -0.34) 140 mg: -1.30 (-1.89; -0.71)
Failed ≥1 medication	-2.64 (-3.34, -1.94)	-3.15 (-3.89; -2.42)	-0.62 (-1.32; 0.08)	70 mg: -2.02 (-2.81, -1.23) 140 mg: -2.54 (-3.35; -1.72)
≥50% MMD responders [c]**-%**				OR[d]
Never failed	46.5%	55.9%	32.6%	70 mg: 1.77(1.16, 2.69) 140 mg: 2.66 (1.76; 4.02)
Failed ≥1 medication	38.6%	39.7%	17.5%	70 mg: 2.93 (1.63, 5.27) 140 mg: 3.06 (1.70; 5.52)
Monthly acute migraine-specific medication days[e] - Mean change[b] (95% CI)				TD
Never failed	-0.91 (-1.20, -0.61)	-1.27 (-1.55; -0.99)	-0.33 (-0.62; -0.04)	70 mg: -0.57 (-0.89, -0.25) 140 mg: -0.94 (-1.25; -0.63)
Failed ≥1 medication	-1.51 (-2.00, -1.01)	-2.16 (-2.68; -1.65)	-0.05 (-0.54; 0.45)	70 mg: -1.46 (-2.02, -0.91) 140 mg: -2.12 (-2.69; -1.55)

CI = confidence interval; MMD = monthly migraine days; TD = treatment difference; OR = odds ratio

[a] MMD at baseline was approximately 8 migraine days per month and similar across the above subgroups.

[b] Least-square mean change from baseline at Month 4-6 and treatment difference are based on a linear mixed effects model including treatment group, baseline monthly value, stratification factors (region [North America versus other and medication overuse [presence versus absence]), scheduled visit and the interaction of treatment group with scheduled visit, without any imputation for missing data.

[c] Responders are defined as patients who achieve ≥50% reduction on MMD from baseline.

[d] Odds ratio for ≥50% responders at Month 4-6 based on a stratified Cochran-Mantel-Haenszel test after missing data were imputed as non-response.

[e] Migraine-specific medications include triptans and ergotamine derivatives.

NON-CLINICAL SAFETY DATA

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.

INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

STORAGE

See folding box.

- Store refrigerated at 2° to 8°C (36˚ to 46˚F) 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 [77°F]) in the original carton and must be used within 14 days. Throw away Pasurta that has been left at room temperature for more than 14 days.
- Do not freeze.
- Do not shake.

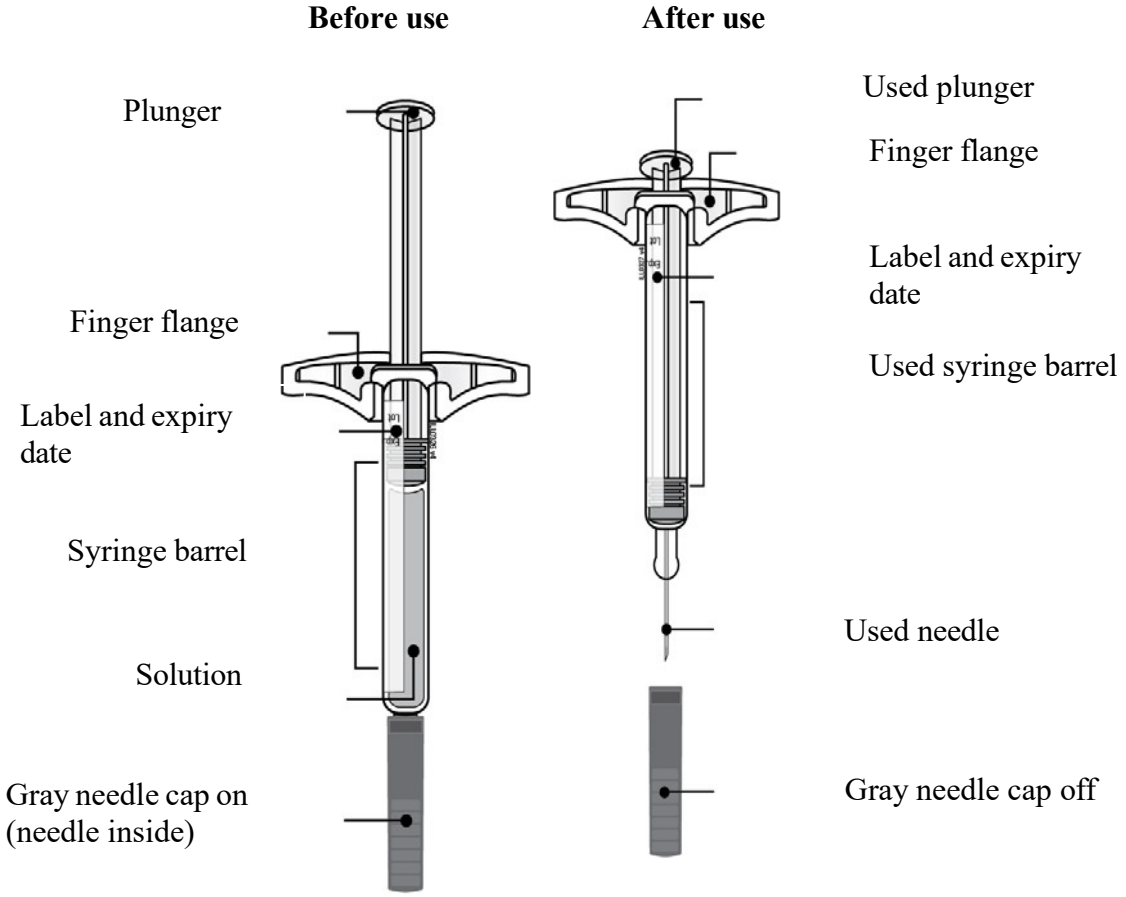
Pasurta should not be used after the date marked “EXP” on the pack.

Pasurta must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Instruction for use of the 70 mg/ml and 140 mg/mL Solution for injection in a Single-Use prefilled Syringe

Single-Use Prefilled Syringe



Important: Needle is inside the grey needle cap.

Important

Before you use an Pasurta prefilled syringe, read this important information:

Storing your Pasurta prefilled syringe

Keep the syringe out of the sight and reach of children.
Keep the syringe in the original carton to protect from light or physical damage.
The syringe should be kept in the refrigerator at 2˚C to 8˚C.
Throw away Pasurta that has been left at room temperature (up to 25°C) for more than 14 days.
Do not store the syringe in extreme heat or cold. For example, avoid storing in your car.
Do not freeze.

Using your Pasurta prefilled syringe

Do not try to inject Pasurta before receiving training from the doctor or nurse.
Do not use a syringe after the expiry date stated on the label.
Do not shake the syringe.
Do not remove the gray needle cap from the syringe until you are ready to inject.
Do not freeze or use the syringe if it has been frozen.
Do not use a syringe if it has been dropped on a hard surface. Part of the syringe may be broken even if you cannot see the break. Use a new syringe, and contact your healthcare provider (doctor, nurse or pharmacist).
This product contains natural rubber latex within the gray needle cap. The product may cause allergic responses in individuals who are sensitized to latex. Tell your healthcare provider if you are allergic to latex.
For more information or help contact your health care provider.

Step 1: Prepare

Read this before you inject.

Check your prescription.

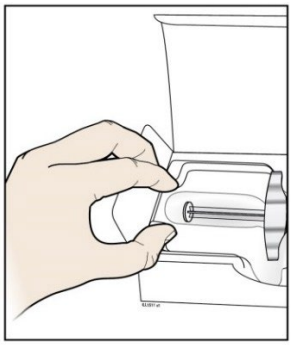
Your healthcare provider has prescribed a 70 mg or 140 mg dose.

For a 70 mg dose, inject one syringe of 70 mg/mL.

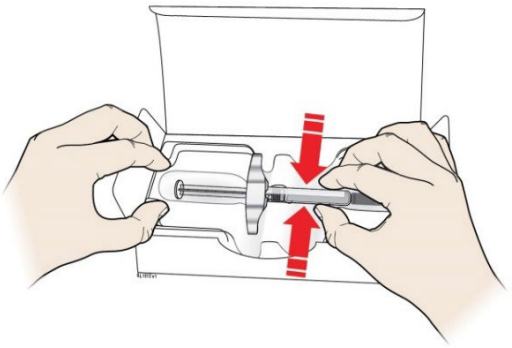
For a 140 mg dose, inject either two syringes of 70 mg/mL one after the other, or one syringe of 140 mg/mL if you were prescribed the 140 mg/mL formulation.

To avoid discomfort at the site of injection, leave the syringe at room temperature for at least 30 minutes before injecting.

A) Remove the Pasurta prefilled syringe(s) from the carton.
Grab the syringe barrel to remove the syringe(s) from the tray.

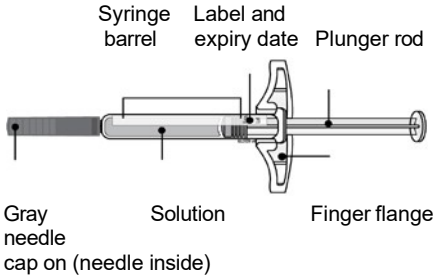


Place your finger and thumb on the edge of the tray to secure it while you remove the syringe(s).



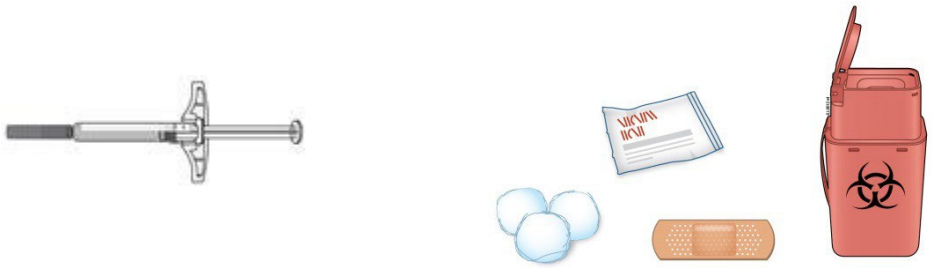
Hold the syringe(s) at the barrel (see arrows).

B) Inspect the Pasurta prefilled syringe(s).
Always hold the syringe(s) **by the syringe barrel.**
Make sure the medicine in the syringe(s) **is clear and colorless to slightly yellow.**
Leave the syringe(s) at room temperature for at least 30 minutes before injecting.
Do not use the syringe(s) if the medicine is cloudy or discolored or contains flakes or particles.
Do not use the syringe(s) if any part appears cracked or broken.
Do not use the syringe(s) if the syringe has been dropped.
Do not use the syringe(s) if the gray needle cap is missing or not securely attached.
Do not use the syringe(s) if the expiry date printed on the label has passed.
In all cases, use a new syringe, and in case of doubts contact your health care provider.



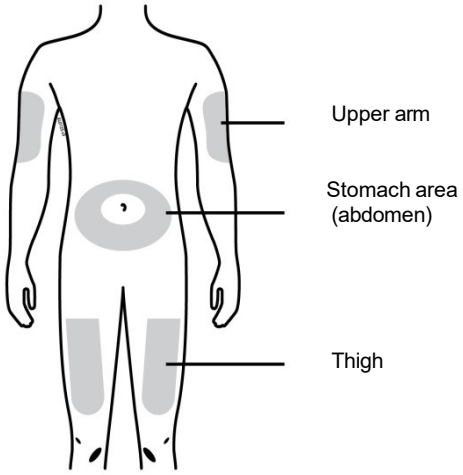
C) Gather all materials needed for the injections. Wash your hands thoroughly with soap and water. On a clean, well-lit work surface, place the:

- One or two new syringes (depending on your prescribed dose)
- Alcohol wipe(s)
- Cotton ball(s) or gauze pad(s)
- Adhesive bandage
- Sharps disposal container



D) Prepare and clean the injection site(s).
Only use these injection sites:

- The thigh
- Stomach area (abdomen), except for a **five** cm area right around the navel
- Outer area of upper arm (only if someone else is giving you the injection)

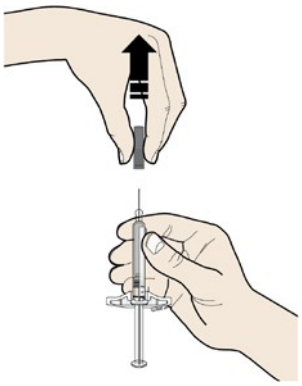


Clean your injection site with an alcohol wipe. Let your skin dry.

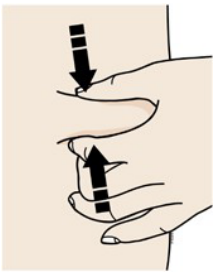
- **Do not** touch this area again before injecting.
- Choose a different site each time you give yourself an injection if you need to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting directly into a raised, thick, red, or scaly skin patch or lesion, or areas with scars or stretch marks.

Step 2: Get ready

E) Pull the gray needle cap straight out and away from your body, only when you are ready to inject.
Do not leave the gray needle cap off for more than five minutes. This can dry out the medicine.
It is normal to see a drop of liquid at the end of the needle.
Do not twist or bend the gray needle cap.
Do not put the gray needle cap back onto the syringe.
Do not remove the gray needle cap from the syringe until you are ready to inject.

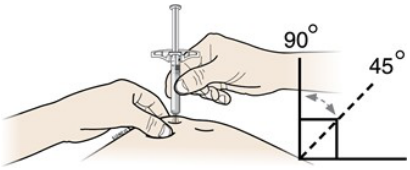


F) Pinch the injection site to create a firm surface.
Pinch skin firmly between your thumb and fingers, creating an area about **five** cm wide.
Important: Keep skin pinched while injecting.

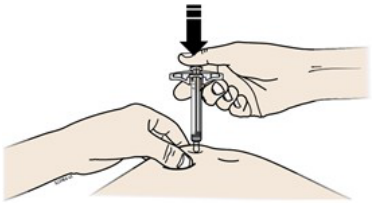


Step 3: Inject

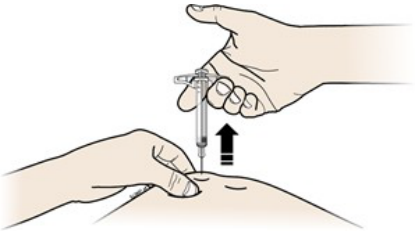
G) While pinching, with the gray needle cap off, insert the syringe into the skin at an angle of 45 to 90 degrees.
Do not place your finger on the plunger rod while inserting the needle.



H) Using slow and constant pressure, push the plunger rod all the way down until it stops moving.



I) When done, release your thumb, and gently lift the syringe off of the skin.



Important: When you remove the syringe, if it looks like the solution is still in the syringe barrel, this means you have not received a full dose. Call your healthcare provider immediately.

Step 4: Finish

J) Discard the used syringe and the gray needle cap.
Put the used Pasurta syringe in a sharps disposal container right away after use**. Do not** throw away (dispose of) the syringe in your household trash.
Talk with your healthcare provider about proper disposal. There may be local regulations for disposal.
Do not reuse the syringe.
Do not recycle the syringe or sharps disposal container or throw them into household trash.
Important: Always keep the sharps disposal container out of the sight and reach of children.

K) Examine the injection site

If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub the injection site. Apply an adhesive bandage if needed.

If you were prescribed the 140 mg dose using two 70 mg/mL syringes, repeat steps 1D to 3 with the second syringe to inject a full dose

Manufacturer:

Amgen Manufacturing Limited

State Road 31, Km 24, 6 Juncos,

Puerto Rico 00777-4060,

Unites States (USA)

Marketing Authorization Holder:

Novartis Nigeria Limited

Landmark Building,

52-54, Isaac John Street,

Ikeja G.R.A

Lagos.