1 NAME OF THE MEDICINAL PRODUCT

VYEPTI

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains eptinezumab 100 mg/mL, available as follows: Injection: 100 mg/mL in a single-dose vial

Excipient(s) with known effect:

This medicinal product contains 40.5 mg of sorbitol in each mL and 0.15 mg of polysorbate 80 in each mL.

For the full list of excipients, see section 11.

3 PHARMACEUTICAL FORM

Concentrate for solution for I.V infusion

VYEPTI is a clear to slightly opalescent, colorless to brownish-yellow solution.

4 INDICATIONS AND USAGE

VYEPTI is indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month.

5 DOSAGE AND ADMINISTRATION

5.1 Recommended Dosing

The recommended dosage is 100 mg administered by intravenous infusion every 3 months. Some patients may benefit from a dosage of 300 mg administered by intravenous infusion every 3 months.

5.2 Dilution Instructions

VYEPTI requires dilution prior to administration. Dilute only in 100 mL 0.9% Sodium Chloride Injection, USP. The infusion bags must be made of polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO). Use appropriate aseptic technique when preparing VYEPTI solution for intravenous infusion. VYEPTI single-dose vials contain no preservative; discard unused portion remaining in the vial.

Dilution

100 mg dose:

To prepare the solution, withdraw 1 mL of VYEPTI from a single-dose vial using a sterile needle and syringe. Inject the 1 mL content into a 100 mL bag of 0.9% Sodium Chloride Injection, USP.

300 mg dose:

To prepare the solution, withdraw 1 mL of VYEPTI from each of 3 single-dose vials using a sterile

needle and syringe. Inject the resulting 3 mL content into a 100 mL bag of 0.9% Sodium Chloride Injection, USP.

Storage and Handling of Diluted Product

Gently invert the VYEPTI solution to mix completely. Do not shake. Following dilution, VYEPTI solution must be infused within 8 hours. During this time, VYEPTI solution should be stored at room temperature or refrigerated at 2 to 8°C.

5.3 Infusion Administration Instructions

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the liquid contains visible particulate matter or is cloudy or discolored *[see QUALITATIVE AND QUANTITATIVE COMPOSITION(2)]*.

No other medications should be administered through the infusion set or mixed with VYEPTI. VYEPTI is for intravenous infusion only; infuse over approximately 30 minutes. Do not administer VYEPTI as an intravenous push or bolus injection. Use an intravenous infusion set with a 0.2 micron or 0.22 micron in-line or add-on sterile filter. After the infusion is complete, flush the line with 20 mL of 0.9% Sodium Chloride Injection, USP.

6 CONTRAINDICATIONS

Hypersensitivity to the active substance (eptinezumab) or to any of the excipients listed in section 11. Reactions have included anaphylaxis and angioedema *[see WARNINGS AND PRECAUTIONS (7.1)]*.

7 WARNINGS AND PRECAUTIONS

7.1 Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema, urticaria, facial flushing, dyspnea and rash, have occurred with VYEPTI in clinical trials and in the postmarketing setting. Most hypersensitivity reactions occurred during infusion and were not serious, but often led to discontinuation or required treatment. Serious hypersensitivity reactions may occur. Cases of anaphylaxis have been reported in the postmarketing setting. If a hypersensitivity reaction occurs, consider discontinuing VYEPTI and institute appropriate therapy *[see CONTRAINDICATIONS (6)]*.

7.2 Hypertension

Development of hypertension and worsening of pre-existing hypertension have been reported following the use of CGRP antagonists, including VYEPTI, in the postmarketing setting. Some of the patients who developed new-onset hypertension had risk factors for hypertension. There were cases requiring initiation of pharmacological treatment for hypertension, and in some cases hospitalization. Hypertension may occur at any time during treatment, but was most frequently reported within 7

days of therapy initiation. The CGRP antagonist was discontinued in many of the reported cases.

Monitor patients treated with VYEPTI for new-onset hypertension or worsening of pre-existing hypertension, and consider whether discontinuation of VYEPTI is warranted if evaluation fails to establish an alternative etiology or blood pressure is inadequately controlled.

7.3 Raynaud's Phenomenon

Development of Raynaud's phenomenon and recurrence or worsening of pre-existing Raynaud's phenomenon have been reported in the postmarketing setting following the use of CGRP antagonists. In reported cases with monoclonal antibody CGRP antagonists, symptom onset occurred a median of 71 days following dosing. Many of the cases reported serious outcomes, including hospitalizations and disability, generally related to debilitating pain. In most reported cases, discontinuation of the CGRP antagonist resulted in resolution of symptoms.

VYEPTI should be discontinued if signs or symptoms of Raynaud's phenomenon develop, and patients should be evaluated by a healthcare provider if symptoms do not resolve. Patients with a history of Raynaud's phenomenon should be monitored for, and informed about the possibility of, worsening or recurrence of signs and symptoms.

7.4 Excipients

VYEPTI contains sorbitol (E420). Patients with hereditary fructose intolerance (HFI) must not be given this medicinal product unless strictly necessary.

A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product

8 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions *[see WARNINGS AND PRECAUTIONS (7.1)]*.
- Hypertension *[see WARNINGS AND PRECAUTIONS (7.2)]*
- Raynaud's Phenomenon *[see WARNINGS AND PRECAUTIONS (7.3)]*

8.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of VYEPTI was evaluated in 2076 patients with migraine who received at least one dose of VYEPTI, representing 1615 patient-years of exposure; of these, 1524 patients were exposed to 100 mg or 300 mg. Across all doses, 1872 patients were exposed for at least 6 months and 991 patients were exposed for 12 months. In the placebo- controlled clinical studies (Study 1 and Study 2) of 1372 patients, 579 patients received at least one dose of VYEPTI100 mg, 574 patients received at least one dose of VYEPTI 300 mg, and 588 patients received placebo *[see CLINICAL STUDIES*

(13)]. Approximately 86% were female, 89% were white, and the mean age was 40.4 years at study entry.

The most common (incidence at least 2% and at least 2% greater than placebo) adverse reactions in the clinical trials for the preventive treatment of migraine were nasopharyngitis and hypersensitivity.

Table 1 summarizes the adverse reactions that occurred during Study 1 and Study 2.

Table 1. Adverse Reactions Occurring with an Incidence of at Least 2% for VYEPTI and at Least 2% Greater than Placebo in Studies 1 and 2

Adverse Reactions	VYEPTI 100 mg N=579 %	VYEPTI 300 mg N=574 %	Placebo N=588 %
Nasopharyngitis	6	8	6
Hypersensitivity reactions*	1	2	0

* Hypersensitivity reactions include multiple related adverse event terms, such as hypersensitivity, pruritus, and flushing/hot flush that occurred on the day of dosing.

In Study 1 and Study 2, 1.9% of patients treated with VYEPTI discontinued treatment because of adverse reactions *[see WARNINGS AND PRECAUTIONS (7.1)]*.

8.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation 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 eptinezumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In patients receiving VYEPTI 100 mg or 300 mg every 3 months, the incidence of anti-eptinezumab antibody development in Study 1 (up to 56 weeks) was 20.6% (92/447), and 41.3% (38/92) of those patients developed anti-eptinezumab neutralizing antibodies. In Study 2 (up to 32 weeks), the incidence of anti-eptinezumab antibody development was 18.3% (129/706), and 34.9% (45/129) of those patients developed anti-eptinezumab neutralizing antibodies. In an open-label study with 84 weeks of treatment, 18% (23/128) of patients developed anti-eptinezumab antibodies, and 39% (9/23) of those patients developed anti-eptinezumab neutralizing antibodies.

Although the results from both studies showed no clear evidence of an impact from development of anti-eptinezumab antibodies, including neutralizing antibodies, on the safety and efficacy profiles of VYEPTI, the available data are too limited to make definitive conclusions.

8.3 POSTMARKETING EXPERIENCE

The following adverse reactions have been identified during postapproval use of VYEPTI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Anaphylaxis *[see CONTRAINDICATIONS (6) and WARNINGS AND PRECAUTIONS (7.1)]*.
General Disorders and Administration Site Conditions: Fatigue
Vascular Disorders: Hypertension *[see WARNINGS AND PRECAUTIONS (7.2)]*,
Raynaud's phenomenon *[see WARNINGS AND PRECAUTIONS (7.3)]*

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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/

9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Risk Summary
There are no adequate data on developmental risks associated with the use of VYEPTI in pregnant women.

No adverse developmental effects were observed following administration of eptinezumab to pregnant animals at doses greater than those used clinically *[see Data]*.

The estimated rate of major birth defects (2.2%-2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk
Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Data
Animal Data

When eptinezumab (0, 75, or 150 mg/kg) was administered weekly to female rats and rabbits by intravenous injection throughout organogenesis, no adverse effects on embryofetal development

were observed. The higher dose tested (150 mg/kg) is 30 times the maximum recommended human dose (MRHD) of 300 mg, on a body weight basis (mg/kg).

When eptinezumab (0, 75, or 150 mg/kg) was administered weekly to female rats throughout pregnancy and lactation, no adverse effects on pre- and postnatal development were observed. The higher dose tested (150 mg/kg) is 30 times the MRHD, on a mg/kg basis.

9.2 Lactation

Risk Summary

There is no data on the presence of eptinezumab in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VYEPTI and any potential adverse effects on the breastfed infant from VYEPTI or from the underlying maternal condition.

9.3 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

9.4 Geriatric Use

Clinical studies of VYEPTI did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

10 DESCRIPTION

Eptinezumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody specific for calcitonin gene-related peptide (CGRP) ligand. Eptinezumab has an approximate molecular weight of 143 kD. Eptinezumab is produced in *Pichia pastoris* yeast cells by recombinant DNA technology.

VYEPTI (eptinezumab) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to brownish-yellow solution, for intravenous infusion. VYEPTI is supplied as a 100 mg/mL single-dose vial. Each mL contains 100 mg eptinezumab formulated in sorbitol, L-histidine monohydrochloride , L-histidine, polysorbate 80
and Water for Injection, USP, at a pH of 5.8.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Eptinezumab is a humanized monoclonal antibody that binds to calcitonin gene-related peptide (CGRP) ligand and blocks its binding to the receptor.

11.2 Pharmacodynamics

The relationship between the pharmacodynamic activity and the mechanism(s) by which eptinezumab exerts its clinical effects is unknown.

11.3 Pharmacokinetics

Eptinezumab exhibits linear pharmacokinetics and exposure increases proportionally with doses from 100 mg to 300 mg after intravenous administration. Steady-state plasma concentration is attained after the first dose with a once every 3-month dosing schedule.

Distribution

The central volume of distribution (Vc) for eptinezumab is approximately 3.7 liters.

Metabolism & Elimination

Eptinezumab is expected to be degraded by proteolytic enzymes into small peptides and amino acids.

The apparent clearance of eptinezumab was 0.006 L/h, and the terminal elimination half-life was approximately 27 days.

Specific Populations

A population pharmacokinetic analysis assessing the effects of age, race, sex, and body weight did not suggest any clinically significant impact of these covariates on eptinezumab exposures.

Patients with Renal or Hepatic Impairment

No dedicated studies were conducted to assess the effects of renal or hepatic impairment on the pharmacokinetics of eptinezumab. However, hepatic or renal impairment is not expected to affect the pharmacokinetics of eptinezumab. A population pharmacokinetic analysis of integrated data from eptinezumab clinical studies did not reveal clinically significant impact on pharmacokinetics of patients with hepatic or renal impairment.

Drug Interaction Studies

P450 Enzymes

Eptinezumab is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Sumatriptan

The co-administration of a single dose of 300 mg eptinezumab administered as an intravenous infusion (over a period of 1 hour ± 15 min) with a single dose of 6 mg sumatriptan administered subcutaneously did not significantly influence the pharmacokinetics of eptinezumab or sumatriptan.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of eptinezumab has not been assessed.

Mutagenesis

Genetic toxicology studies of eptinezumab have not been conducted.

Impairment of Fertility

When eptinezumab (0, 75, or 150 mg/kg) was administered weekly by intravenous injection to male and female rats prior to and during mating and continuing in females to gestation day 3-4, no adverse effects on fertility were observed. The higher dose tested (150 mg/kg) is 30 times the maximum recommended human dose of 300 mg, on a body weight basis (mg/kg).

13 CLINICAL STUDIES

The efficacy of VYEPTI was evaluated as a preventive treatment of episodic and chronic migraine in two randomized, multicenter, placebo-controlled studies, both with 6-month double-blind periods: one study in patients with episodic migraine (Study 1) and one study in patients with chronic migraine (Study 2). VYEPTI was administered by intravenous infusion every 3 months in both studies; however, the primary endpoint was measured at 12 weeks.

Study 1: Episodic Migraine

Study 1 (NCT02559895) included adults with a history of episodic migraine (4 to 14 headache days per month, of which at least 4 were migraine days). A total of 665 patients were randomized to receive placebo (N=222), 100 mg VYEPTI (N=221), or 300 mg VYEPTI (N=222) every 3 months for 12 months. Patients were allowed to use concurrent acute migraine or headache medications, including migraine-specific medications (i.e., triptans, ergotamine derivatives), during the trial.

The study excluded patients with a history of cardiovascular disease (hypertension, ischemic heart disease), neurological disease, or cerebrovascular disease.

The primary efficacy endpoint was the change from baseline in mean monthly migraine days over Months 1-3. Secondary endpoints included the percentages of patients with 50% or greater, and 75% or greater reductions from baseline in monthly migraine days over Months 1-3.

Patients had a median age of 39 years (range: 18 to 71 years), 84% were female, and 84% were white. The mean migraine frequency at baseline was approximately 8.6 migraine days per month and was similar across treatment groups.

VYEPTI treatment demonstrated statistically significant improvements compared to placebo for the primary efficacy endpoint, as shown in Table 2; secondary endpoints are also summarized in Table 2.

Table 2. Efficacy Endpoint Results in Study 1

	VYEPTI 100 mg N=221	VYEPTI 300 mg N=222	Placebo N=222
Monthly Migraine Days (MMD) – Months 1-3			
Change from baseline	-3.9	-4.3	-3.2
Difference from placebo	-0.7	-1.1	
p-value	0.018	<0.001	
≥50% MMD responders – Months 1-3			
% Responders	49.8%	56.3%	37.4%
Difference from placebo	12.4%	18.9%	
p-value	0.009*	<0.001	
≥75% MMD responders – Months 1-3			
% Responders	22.2%	29.7%	16.2%
Difference from placebo	6.0%	13.5%	
p-value	NS**	<0.001	

* Nominal statistical significance
** NS = Not statistically significant

Figure 1 shows the mean change from baseline in average monthly migraine days in Study 1. Patients treated with VYEPTI at both doses had greater mean decreases from baseline in mean monthly migraine days over Months 1-3 compared to placebo-treated patients.

Figure 1. Change from Baseline in Monthly Migraine Days in Study 1

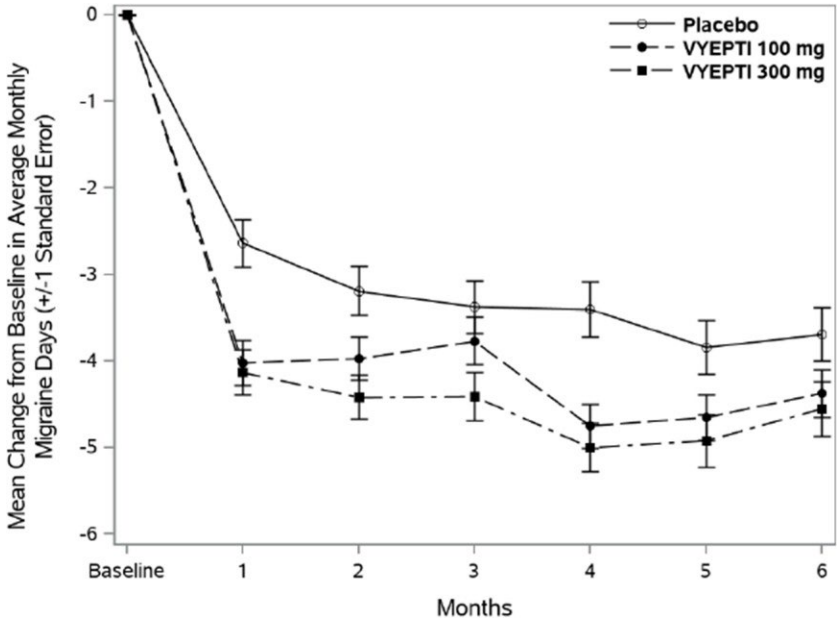


Figure 2 shows the distribution of change from baseline in mean monthly migraine days through Month 3 by treatment group in 2-day increments.

Figure 2. Distribution of Change from Baseline in Mean Monthly Migraine Days over Months 1 to 3 by Treatment Group in Study 1

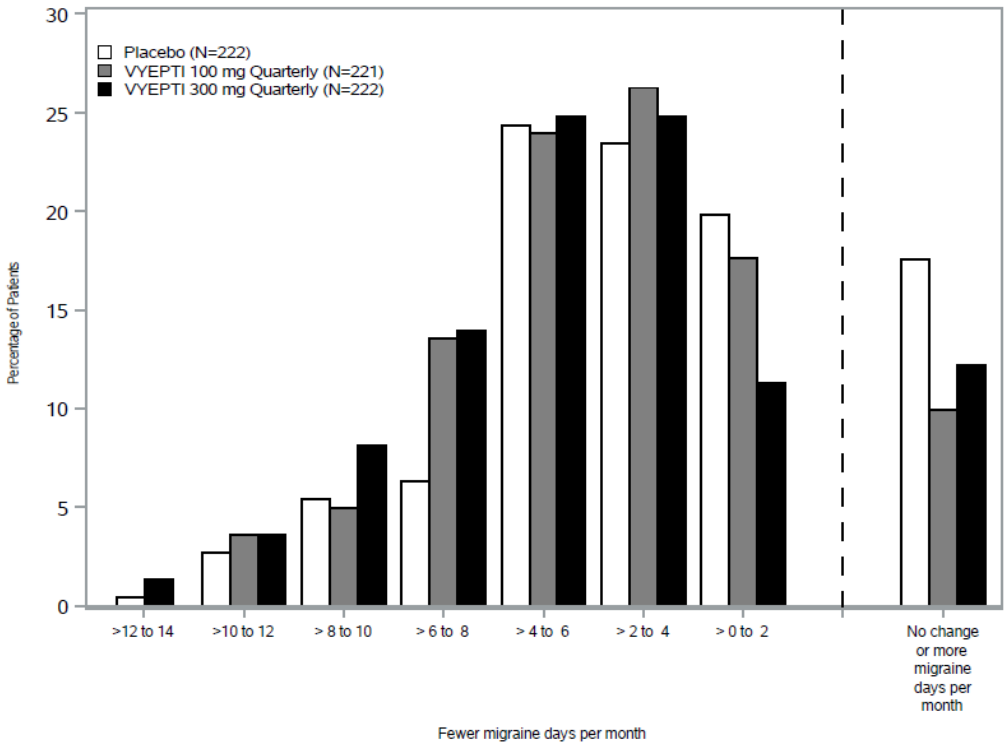
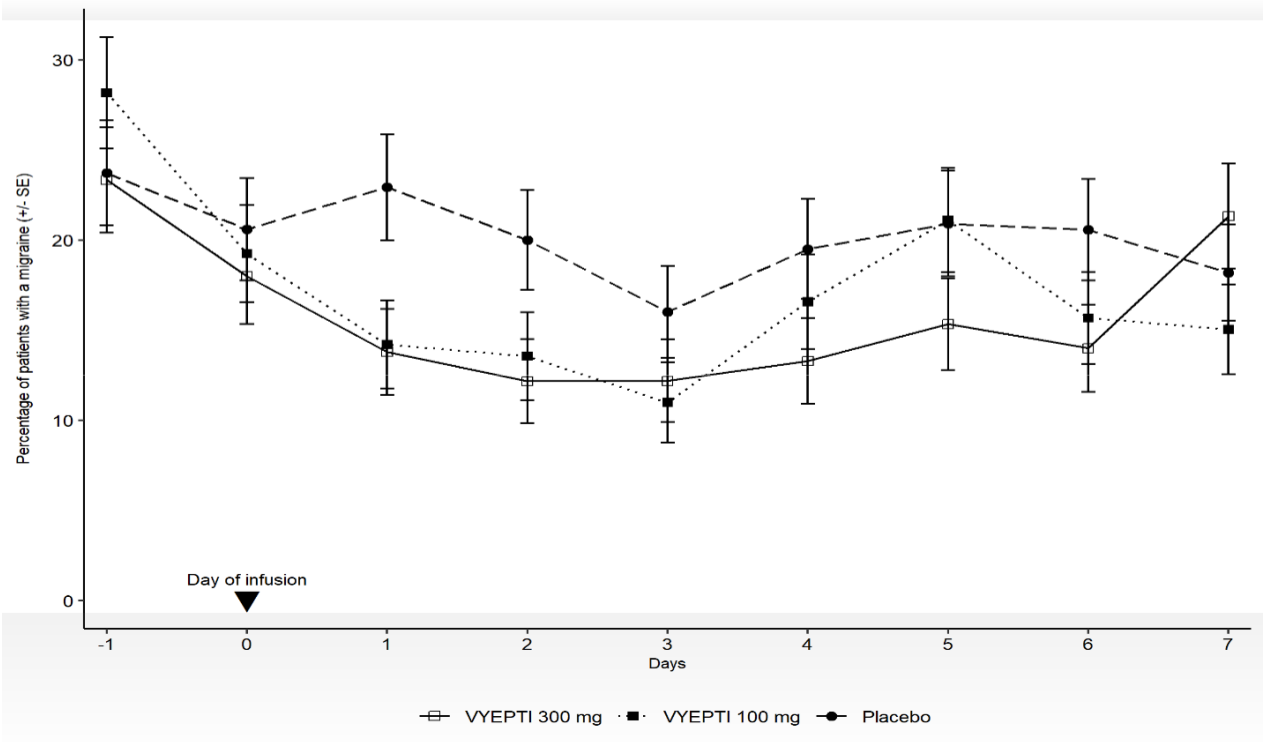


Figure 3 demonstrates that greater percentages of placebo-treated patients had migraines on most days during the first 7 days of treatment compared to VYEPTI-treated patients in Study 1.

Figure 3. Percentage of Patients with a Migraine from Day -1 (Day Prior to Infusion) to Day 7 in Study 1



Study 2: Chronic Migraine

Study 2 (NCT02974153) included adults with a history of chronic migraine (15 to 26 headache days per month, of which at least 8 were migraine days). A total of 1072 patients were randomized and received placebo (N=366), 100 mg VYEPTI (N=356), or 300 mg VYEPTI (N=350) every 3 months for 6 months. Patients were allowed to use and to continue an established stable regimen of acute migraine or headache preventive medication (except onabotulinumtoxinA). Patients with a dual diagnosis of chronic migraine and medication overuse headache attributable to acute medication overuse (triptans, ergotamine, or combination analgesics greater than 10 days per month) were included in the study population.
Patients using opioids or butalbital-containing products greater than 4 days per month were not allowed.

The study excluded patients with a history of cardiovascular disease (hypertension, ischemic heart disease), neurological disease, or cerebrovascular disease.

The primary efficacy endpoint was the change from baseline in mean monthly migraine days over Months 1-3. Secondary endpoints included the percentages of patients with 50% or greater and 75% or greater reductions from baseline in monthly migraine days over Months 1-3.

Patients had a median age of 41 years (range: 18 to 65 years), 88% were female, and 91% were white. Forty-one percent of patients were taking concomitant preventive medication for migraine. The mean migraine frequency at baseline was approximately 16.1 migraine days per month and was similar across treatment groups.

VYEPTI treatment demonstrated statistically significant improvements compared to placebo for the primary efficacy endpoint, as shown in Table 3; secondary endpoints are also summarized in Table 3.

Table 3. Efficacy Endpoint Results in Study 2

	VYEPTI 100 mg N=356	**VYEPTI 300 mg N=350**	**Placebo N=366**
Monthly Migraine Days (MMD) – Months 1-3			
Change from baseline	-7.7	-8.2	-5.6
Difference from placebo	-2.0	-2.6	
p-value	<0.001	<0.001	
≥50% MMD responders – Months 1-3			
% Responders	57.6%	61.4%	39.3%
Difference from placebo	18.2%	22.1%	

p-value	<0.001	<0.001	
≥75% MMD responders – Months 1-3			
% Responders	26.7%	33.1%	15.0%
Difference from placebo	11.7%	18.1%	
p-value	<0.001	<0.001	

Figure 4 shows the mean change from baseline in average monthly migraine days for Study 2. Patients treated with VYEPTI at both doses had greater mean decreases from baseline in mean monthly migraine days over Month 1-3 compared to placebo-treated patients.

Figure 4. Change from Baseline in Monthly Migraine Days in Study 2

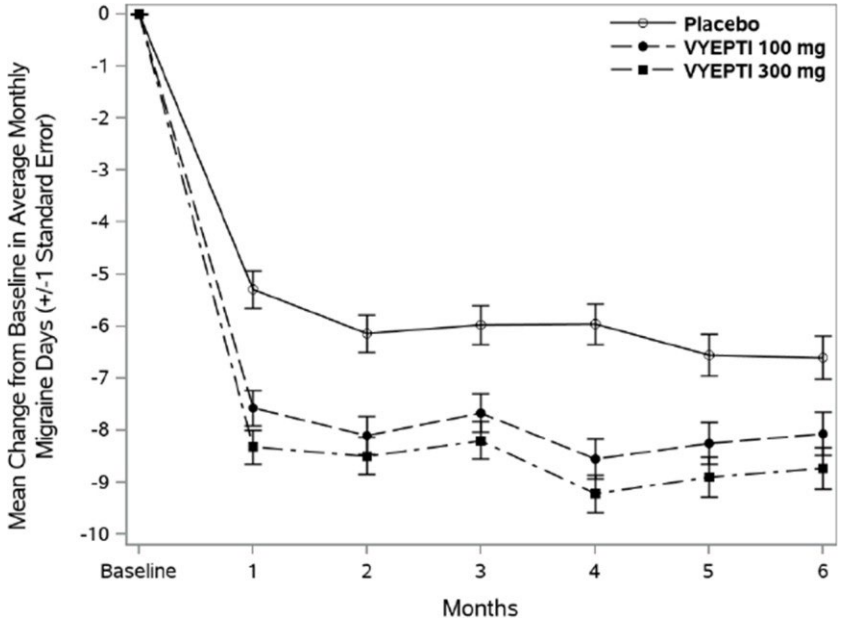


Figure 5 shows the distribution of change from baseline in mean monthly migraine days through Month 3 by treatment group in 3-day increments.

Figure 5. Distribution of Change from Baseline in Mean Monthly Migraine Days over Months 1-3 by Treatment Group in Study 2

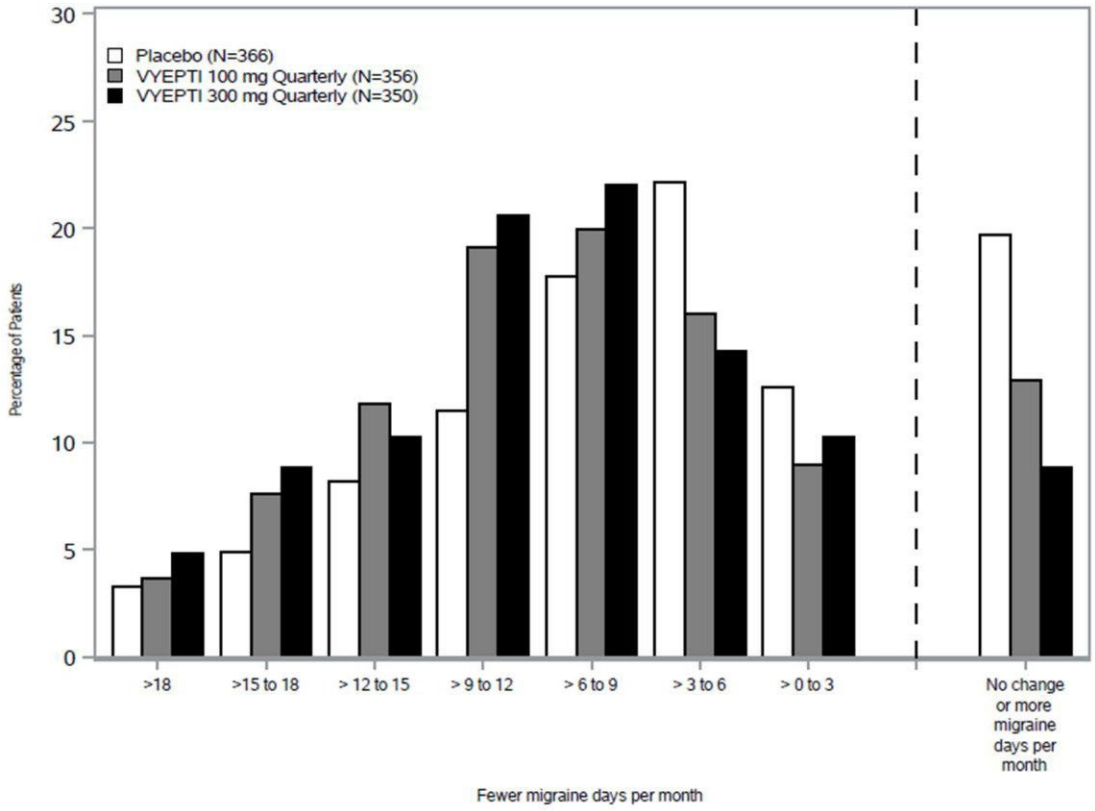
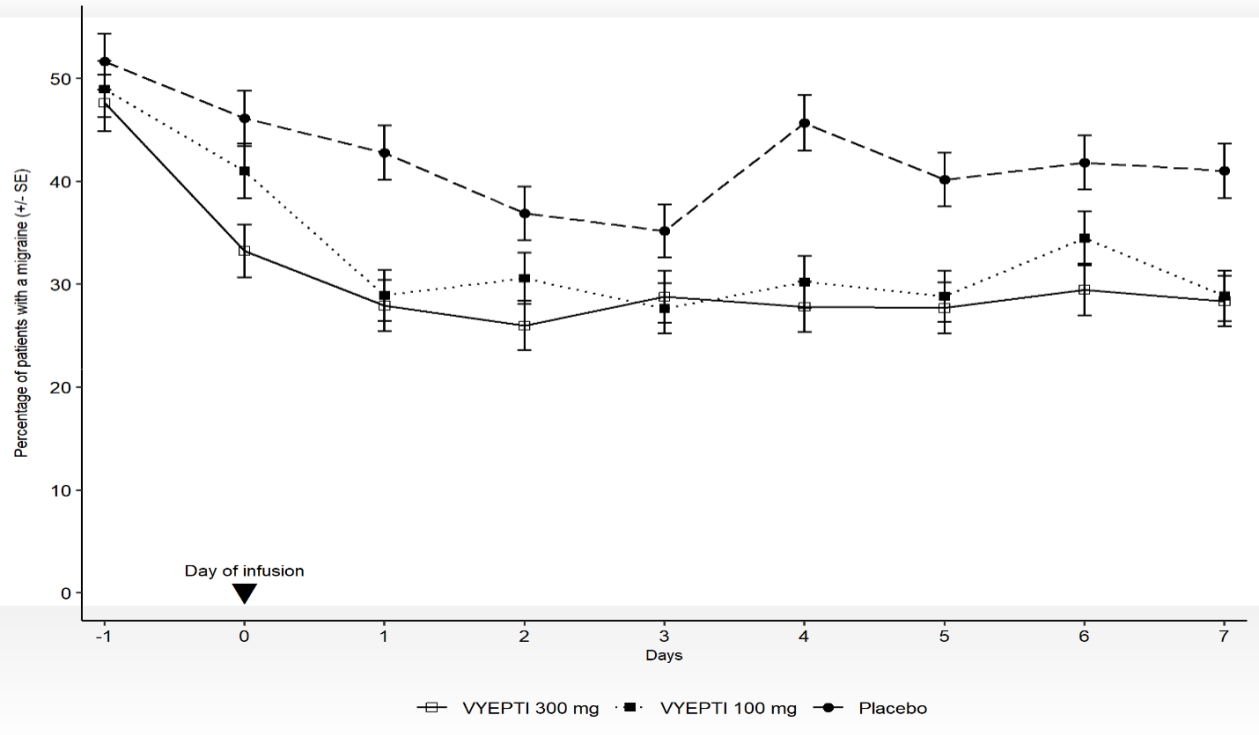


Figure 6 demonstrates that greater percentages of placebo-treated patients had migraines on individual days during the first 7 days of treatment compared to VYEPTI-treated patients in Study 2.

Figure 6. Percentage of Patients with a Migraine from Day -1 (Day Prior to Infusion) to Day 7 in Study 2



14 HOW SUPPLIED/STORAGE AND HANDLING

14.1 How Supplied

VYEPTI (eptinezumab) injection is a clear to slightly opalescent, colorless to brownish-yellow solution supplied as: Carton containing one 100 mg/mL single-dose type I glass vial, with gray chlorobutyl rubber and flip-off aluminum seal.

14.2 Shelf life

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

14.3 Storage and Handling

Store refrigerated at 2°C to 8°C in the original carton to protect from light until time of use. Do not freeze or shake.

15. Manufacturer: H. Lundbeck A/S, Ottiliavej 9, DK-2500 Valby, Denmark

16. License Holder: LUNDBECK ISRAEL LTD., 11 Galgaley Haplada, P.O.B. 13105, Herzliya 4672211

17. Registration Number: 168-65-36769-00

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