PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrVYEPTI®

(Eptinezumab for injection)

Solution for intravenous infusion
100 mg/mL

Professed Standard

Calcitonin gene-related peptide (CGRP) binding antibody

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VYEPTI® (eptinezumab for injection) is indicated for the prevention of migraine in adults who have at least 4 migraine days per month.

VYEPTI should be prescribed by healthcare professionals experienced in the diagnosis and treatment of migraine.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available in the pediatric population (< 18 years of age); therefore, VYEPTI is not authorized for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): The safety and efficacy of VYEPTI has not been established in patients aged 65 or older. The clinical study program of VYEPTI did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients (see Section 7.1.5 Geriatrics).

2 CONTRAINDICATIONS

VYEPTI is contraindicated in patients who are hypersensitive to eptinezumab or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container (For a complete listing, see Section 5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

VYEPTI should be administered as an intravenous infusion only.
VYEPTI requires dilution prior to administration (see Section 3.4 DILUTION INSTRUCTIONS).

3.2 Recommended Dose and Dosage Adjustment

The recommended dose is 100 mg administered by intravenous infusion every 12 weeks. Some patients may benefit from a dosage of 300 mg administered by intravenous infusion every 12 weeks. (see Section 14.2 STUDY RESULTS).

The need for dose escalation should be assessed within 12 weeks after initiation of the treatment.

When switching dosage options, the first dose of the new regimen should be given on the next scheduled dosing date of the prior regimen.

The treatment benefit should be assessed 3-6 months after initiation of the treatment.

Any further decision to continue the treatment should be made on an individual patient basis and determined prior to each dose. (see PART II. CLINICAL TRIALS).

VYEPTI is not authorized for pediatric use (see Section 1.1 INDICATIONS).

3.3 Administration

VYEPTI is for intravenous infusion only.
VYEPTI requires dilution prior to administration (see Section 3.4 DILUTION INSTRUCTIONS).

VYEPTI must be administered by a healthcare professional.

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 Section 5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING].

No other medications should be administered through the infusion set or mixed with VYEPTI. Do not administer VYEPTI as an intravenous bolus injection.

Use an intravenous infusion set with a 0.2 or 0.22 µm in-line or add-on filter. After the infusion is complete, flush the line with 20 mL of 0.9% Sodium Chloride for Injection (see Section 3.4 DILUTION INSTRUCTIONS).

Following dilution of the vial content in a 100 mL bag of 0.9% Sodium Chloride for Injection (see Section 3.4 DILUTION INSTRUCTIONS), infuse VYEPTI 100 mg or 300 mg as prescribed over approximately 30 minutes.

3.4 Dilution Instructions

Parenteral Products: Each vial of VYEPTI is intended for single use only.

Preparation instructions:
Use appropriate aseptic technique when preparing VYEPTI solution for intravenous infusion. The product contains no preservative and is intended for single use only.

VYEPTI is a sterile, clear to slightly opalescent, colourless to brownish-yellow solution. Prior to dilution, the solution in the vials should be inspected visually; do not use if the solution contains visible particulate matter or is cloudy or discoloured (other than clear to slightly opalescent, colourless to brownish-yellow).

For both the 100 mg and the 300 mg dose, a 100 mL bag of 0.9% Sodium Chloride for Injection should be used to prepare the VYEPTI infusion solution as described below. No other IV diluents or volume may be used to prepare the VYEPTI infusion solution.

Gently invert the solution to mix completely. Do not shake.

Following dilution, VYEPTI infusion solution must be infused within 8 hours. During this time, VYEPTI infusion solution may be stored at room temperature or refrigerated at 2 to 8°C. If

stored at 2 to 8°C, allow the solution to warm to room temperature prior to infusion. DO NOT FREEZE.

100 mg dose:
To prepare the solution, withdraw 1.0 mL of VYEPTI from a single-use vial using a sterile needle and syringe. Inject the 1.0 mL (100 mg) content into a 100 mL bag of 0.9% Sodium Chloride for Injection.

300 mg dose:
To prepare the solution, withdraw 1.0 mL of VYEPTI from each of 3 single-use vials using a sterile needle and syringe. Inject the resulting 3.0 mL (300 mg) content into a 100 mL bag of 0.9% Sodium Chloride for Injection.

3.5 Missed Dose

In case of a missed dose, resume the regular dosing schedule as soon as possible.

4 OVERDOSAGE

There has been no experience of overdose with eptinezumab. Doses up to 1000 mg have been administered intravenously to humans without tolerability issues or clinically significant adverse reactions.

In the event of an overdose, it is recommended that the patient should be monitored for any signs or symptoms of adverse reactions and appropriate supportive treatment be available for institution immediately if needed.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	100 mg/mL solution in a single use vial	Sorbitol, L-histidine, L-histidine monohydrochloride, polysorbate 80 and water for injection

VYEPTI is a clear to slightly opalescent, colourless to brownish-yellow, sterile, preservative-free concentrate to be diluted in a 100 mL bag of 0.9% Sodium Chloride for Injection prior to infusion.

Each single-use glass vial contains 100 mg of eptinezumab in 1 mL solution. Each carton contains one vial.

6 DESCRIPTION

VYEPTI contains the active ingredient eptinezumab which is a humanized monoclonal immunoglobulin G1 (IgG1) antibody that binds with high affinity to α- and β- forms of human calcitonin gene-related peptide (CGRP) ligand to prevent activation of CGRP receptors.

7 WARNINGS AND PRECAUTIONS

Serious Hypersensitivity
Serious hypersensitivity reactions, including angioedema, urticaria, rash and anaphylactic reactions have been reported with the class products including VYEPTI in clinical trials and may develop within minutes of the infusion. If a serious hypersensitivity reaction occurs, administration of VYEPTI should be discontinued immediately and appropriate therapy initiated.

Patients with Cardiovascular Diseases:
No safety data are available in these populations. Patients with a known history or evidence of arteriosclerosis, cardiomyopathy, coronary artery disease, serious heart rhythm abnormalities, hypertension, cerebrovascular disease, Raynaud's disease, and/ or any active, progressive or unstable cardiovascular disorder were excluded from the clinical trials. (see PART II: CLINICAL TRIALS)

Patients with diabetes, morbid obesity, neurological or autoimmune disorder:
Limited safety data are available in these populations. Patients with a known history or evidence of diabetes or any active, progressive or unstable neurological or autoimmune disorder were excluded from the clinical trials (See PART II: CLINICAL TRIALS)

Hepatic or Renal Insufficiency:
No dedicated hepatic or renal impairment studies were conducted to assess the effects of hepatic and renal impairment upon the pharmacokinetics of eptinezumab (see Section 10.3 Pharmacokinetics).

Patients with HIV, Hepatitis B and C:
No safety data are available in these populations. Patients with a known history or screened positive for any of these infections were excluded from the clinical trials.

Fertility:
The effect of eptinezumab on human fertility has not been evaluated.

7.1 Special Populations

7.1.1 Pregnant Women

There is a very limited amount of data from the use of eptinezumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Section 15 NON-CLINICAL TOXICOLOGY). Human IgG is known to cross the placental barrier; therefore, eptinezumab may be transmitted from the mother to the developing fetus.

VYEPTI has a half-life of approximately 29 days (see CLINICAL PHARMACOLOGY). This should be taken into consideration for women who are pregnant or plan to become pregnant while using VYEPTI (see NON-CLINICAL TOXICOLOGY).

VYEPTI should not be used by pregnant women unless the expected benefit to the mother justifies the potential risk to the fetus.

7.1.2 Breast-feeding

There are no data on the presence of eptinezumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be excreted in breast milk; therefore, eptinezumab may be transmitted from the mother to the breastfed infant. 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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available in the pediatric population (< 18 years of age); therefore, VYEPTI is not authorized for pediatric use.

7.1.4 Geriatrics

The clinical study program of VYEPTI did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of VYEPTI has been evaluated in more than 2,000 patients with migraine who received at least one dose of VYEPTI, representing more than 1,600 patient-years of exposure; of these, approximately 1,500 patients were exposed to 100 mg or 300 mg. Across all doses, 1872 patients were exposed for at least 24 weeks and 991 patients were exposed for 48 weeks. Approximately 86% were female and the mean age was 40.4 years at study entry.

Patients with a history of cardiovascular disease (hypertension, ischemic heart disease), neurological disease, cerebrovascular disease, morbid obesity and diabetes, alcohol/drug abuse, and severe mental disorders were excluded from clinical studies.

Table 2: Adverse Reactions Reported with VYEPTI-treated Patients (and More Frequently than in Patients Receiving Placebo) by System Organ Class and Preferred Term

System Organ Class/ Preferred Term	VYEPTI 100 mg every 12 weeks N=579 n (%)	VYEPTI 300 mg every 12 weeks N=574 n (%)	Placebo N=588 n (%)
Infections and Infestations			
Nasopharyngitis	36 (6.2)	47 (8.2)	34 (5.8)
Immune System Disorders			
Hypersensitivity reactions	15 (2.6)	22 (3.8)	7 (1.2)

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in clinical practice. The adverse reaction rates should not be compared to the rates in clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In the placebo-controlled pivotal clinical studies (PROMISE 1 and PROMISE 2) of 1,372 patients, 579 patients received at least one dose of VYEPTI 100 mg, 574 patients received at least one dose of VYEPTI 300 mg, and 588 patients received placebo during 24 weeks or 48 weeks of double-blind treatment.
In the pivotal studies, the following adverse events in Table 3 were observed to occur at or above 1% and greater than placebo during the double-blind treatment phase.

Table 3: Incidence of Treatment-emergent Adverse Events in ≥ 1 % of Subjects with Episodic Migraine and Chronic Migraine in either VYEPTI Group (100 mg or 300 mg) and greater than placebo

System Order Class Preferred Term	VYEPTI 100 mg N= 579 n (%)	VYEPTI 300 mg N= 574 n (%)	Placebo N= 588 n (%)
Ear and labyrinth disorders			
Vertigo	6 (1.0)	2 (0.3)	6 (1.0)
Gastrointestinal disorders			
Constipation	4 (0.7)	7 (1.2)	2 (0.3)
Diarrhoea	6 (1.0)	11 (1.9)	4 (0.7)
Nausea	11 (1.9)	17 (3.0)	15 (2.6)
Vomiting	4 (0.7)	9 (1.6)	7 (1.2)
General Disorders and administration site conditions			
Fatigue	16 (2.8)	14 (2.4)	8 (1.4)
Hepatobiliary disorders			
Cholelithiasis	6 (1.0)	1 (0.2)	0
Immune system disorders			
Hypersensitivity	1 (0.2)	8 (1.4)	0
Infections and infestations			
Gastroenteritis	6 (1.0)	5 (0.9)	5 (0.9)
Gastroenteritis viral	7 (1.2)	5 (0.9)	5 (0.9)
Influenza	5 (0.9)	18 (3.1)	14 (2.4)
Nasopharyngitis	36 (6.2)	47 (8.2)	34 (5.8)
Upper respiratory tract infection	37 (6.4)	42 (7.3)	36 (6.1)
Urinary tract infection	11 (1.9)	16 (2.8)	9 (1.5)
Injury, poisoning and procedural complications			
Muscle strain	6 (1.0)	2 (0.3)	2 (0.3)
Investigations			
Blood pressure increased	6 (1.0)	3 (0.5)	4 (0.7)
Weight increased	7 (1.2)	3 (0.5)	2 (0.3)
Musculoskeletal and connective tissue disorders			
Arthralgia	10 (1.7)	14 (2.4)	9 (1.5)

Back pain	14 (2.4)	9 (1.6)	13 (2.2)
Nervous system disorders			
Dizziness	15 (2.6)	13 (2.3)	12 (2.0)
Psychiatric disorders			
Anxiety	7 (1.2)	7 (1.2)	2 (0.3)
Depression	6 (1.0)	8 (1.4)	6 (1.0)
Insomnia	5 (0.9)	8 (1.4)	7 (1.2)
Respiratory, thoracic and mediastinal disorders			
Cough	10 (1.7)	12 (2.1)	7 (1.2)
Oropharyngeal pain	6 (1.0)	6 (1.0)	3 (0.5)
Rhinorrhoea	7 (1.2)	4 (0.7)	0
Skin and subcutaneous tissue disorders			
Rash	1 (0.2)	7 (1.2)	3 (0.5)

Nasopharyngitis
Nasopharyngitis was most frequent after the first dose of VYEPTI at any dose. The incidence decreased with subsequent doses and was stable thereafter.

Infusion site reactions
Infusion site-related adverse events occurred infrequently and in similar proportions of VYEPTI and placebo patients (< 2%) with no apparent relationship to VYEPTI dose. The most frequently occurring infusion-site related adverse event was infusion site extravasation, which occurred in < 1% of VYEPTI and placebo patients in pivotal trials. Other infusion site reactions include infusion site rash and infusion site pain. The infusion site reactions were non-serious and most occurred on the day of infusion.

Hypersensitivity reactions
Approximately 4% of patients on 300 mg, 3% of patients on 100 mg and 1% of patients on placebo in PROMISE 1 and PROMISE 2 experienced hypersensitivity reactions. The reactions were reported with multiple related adverse event terms, such as hypersensitivity, angioedema, urticaria, flushing/hot flush, rash and pruritus. Most hypersensitivity reactions occurred during infusion and were not serious.

8.3 Less Common Clinical Trial Adverse Reactions

From all placebo-controlled clinical trials with VYEPTI in adult patients with migraine, the following less common adverse events of <1% have been observed. Causality related to treatment with VYEPTI has not been established.

Eye disorders: vision blurred
Gastrointestinal disorders: dry mouth
General disorders and administrative site conditions: asthenia
Metabolism and nutrition disorders: decreased appetite
Nervous system disorders: migraine, lethargy, memory impairment
Psychiatric disorders: abnormal dreams
Reproductive system and breast disorders: menorrhagia
Respiratory, thoracic and mediastinal disorders: nasal congestion, asthma
Skin and subcutaneous tissue disorders: pruritus generalized

8.4 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The methodology for detection of antibody formation is highly dependent on several factors, e.g. sample handling and the sensitivity and specificity of the assay. Thus, 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 placebo-controlled pivotal clinical studies, PROMISE 1 (up to 56 weeks) and PROMISE 2 (up to 32 weeks), the incidence of anti-eptinezumab antibodies across both studies was 18% (105/579) and 20% (115/574) in patients receiving 100 mg and 300 mg every 12 weeks dosing, respectively. In both studies, the incidence of anti-eptinezumab antibodies peaked at Week 24. The incidence of neutralizing antibodies across both studies was 8.3% (48/579) and 6.1% (35/574) for the 100 mg and 300 mg treatment groups, respectively.

In an open-label study with 84 weeks of treatment of 300 mg eptinezumab every 12 weeks, 18% (23/128) of patients developed anti-eptinezumab antibodies with an overall incidence of neutralizing antibodies of 7% (9/128). Eptinezumab trough plasma concentrations appeared lower in patients who developed anti-eptinezumab antibodies.

There was no evidence of impact of anti-eptinezumab antibody development on efficacy or safety in the clinical studies.

8.5 Post-Market Adverse Reactions

Not available.

9 DRUG INTERACTIONS

9.1 Overview

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

9.2 Drug-Drug Interactions

Sumatriptan
The co-administration of a single dose of 300 mg eptinezumab in combination with a single dose of 6 mg sumatriptan administered subcutaneously did not alter the pharmacokinetics of eptinezumab or sumatriptan in healthy subjects.

Interactions with other drugs have not been studied.

9.3 Drug-Food Interactions

Not relevant as VYEPTI is administered intravenously.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Eptinezumab is a humanized immunoglobulin G1 (IgG1) antibody that binds to human-calcitonin gene-related peptide (CGRP) ligand with picomolar affinity and blocks its binding to the CGRP receptors.

Eptinezumab is highly selective and does not bind to any of the related neuropeptides amylin, calcitonin, adrenomedullin and intermedin.

10.2 Pharmacodynamics

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

10.3 Pharmacokinetics

Eptinezumab exhibits linear pharmacokinetics and exposure increases proportionally with intravenous doses from 100 to 300 mg.

Following the dose regimens of 100 mg and 300 mg every 12 weeks, steady-state was attained within 24 weeks. The mean accumulation ratios based on C_{max} and $AUC_{0\text{-}tau}$ are 1.08 and 1.15, respectively, based on a population pharmacokinetics analysis. Pharmacokinetic exposure parameter values for eptinezumab are included in Table 4. The steady-state $AUC_{0\text{-}tau}$ of eptinezumab was estimated to be 52% lower in a 190 kg subject (heaviest subject in clinical trials) and 51% higher in a 39 kg subject (lightest subject in clinical trials) compared to a 70 kg subject.

Table 4: Summary of Pharmacokinetic Parameters of Eptinezumab at Steady State

Pharmacokinetic Parameters	VYEPTI 100 mg every 12 weeks	VYEPTI 300 mg every 12 weeks
C_{max}[a], mean (SD) [b]	40.9 (10.9) µg/mL	125 (36.5) µg/mL
$AUC_{0\text{-}tau}$[c], mean (SD)[b]	867 (278) day·µg/mL	2629 (791) day·µg/mL

[a] C_{max} = the maximum concentration
[b] SD = Standard deviation
[c] $AUC_{0\text{-}tau}$ = area under the concentration-time curve during a dosing interval (12 weeks) following 30 to 60-minute IV infusion

Absorption: VYEPTI is administered by intravenous infusion which bypasses extravascular absorption and is 100% bioavailable. Median time to peak concentration was attained at the end of infusion (30 minutes).

Distribution: The volume of distribution for eptinezumab was approximately 4.8 L in chronic migraine and episodic migraine patients, based on a population pharmacokinetics analysis.

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

Elimination: The systemic clearance was 0.12 L/day (CV 34%), and the terminal elimination half-life was approximately 29 days in chronic migraine and episodic migraine patients, based on a population pharmacokinetics analysis.

Special Populations and Conditions:
The pharmacokinetics of eptinezumab were not significantly impacted by age, sex, or race based on a population pharmacokinetics analysis.

Hepatic or Renal Insufficiency:
No dedicated hepatic or renal impairment studies were conducted to assess the effects of hepatic and renal impairment upon the pharmacokinetics of eptinezumab. Population pharmacokinetic analysis revealed that hepatic or renal impairment did not have any significant impact on the pharmacokinetics of eptinezumab. Patients with severe renal impairment (creatinine clearance <30 mL/min) have not been studied.

11 STORAGE, STABILITY AND DISPOSAL

Store refrigerated at 2 to 8°C. Keep the vial in the outer carton in order to protect from light. Do not freeze or shake.

Following dilution, VYEPTI solution (VYEPTI and 0.9% Sodium Chloride for Injection) must be infused within 8 hours. During this time, VYEPTI solution may be stored at room temperature or refrigerated at 2 to 8°C. If stored at 2 to 8°C, allow the solution to warm to room temperature prior to infusion.

Any unused medicinal product or waste material should be disposed.

12 SPECIAL HANDLING INSTRUCTIONS

VYEPTI should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution.

Do not use if the solution contains visible particulate matter or is cloudy or discolored (other than clear to slightly opalescent, colorless to brownish-yellow).

No other IV diluents than 0.9% Sodium Chloride for Injection (100 mL) may be used to prepare the VYEPTI solution.

Do not freeze or shake.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Eptinezumab for injection
Chemical name:	Immunoglobulin G1, anti-(calcitonin gene-related peptide) (human-Oryctolagus cuniculus monoclonal ALD403 heavy chain), disulfide with human-Oryctolagus cuniculus monoclonal ALD403 κ-chain, dimer.
Molecular mass:	Eptinezumab has an approximate molecular mass of 143 kDa
Structural formula:	Eptinezumab is an IgG1 kappa immunoglobin containing human constant region sequences. The light and heavy chain variable regions are comprised of both human and humanized rabbit sequences. Eptinezumab is composed of two heavy chains of 441 amino acids and two light chains of 219 amino acids.
Physicochemical properties:	VYEPTI® is supplied as a sterile, nonpyrogenic, preservative free aqueous solution of eptinezumab for intravenous administration after dilution. VYEPTI is clear to slightly opalescent, colorless to brownish-yellow colored solution with a pH of 5.8.
Product Characteristics :	Eptinezumab is a humanized monoclonal immunoglobulin G1 (IgG1) antibody directed against the human α-and β-forms of calcitonin gene-related peptide (produced in a yeast-based (Pichia pastoris) expression system.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

VYEPTI was evaluated for the prevention of migraine in two pivotal studies (Table 5): PROMISE 1 was conducted in patients with episodic migraine (n=888) and PROMISE 2 in patients with chronic migraine (n=1072). Both studies excluded patients with a known history of cardiovascular disease (hypertension, ischemic heart disease), neurological disease, cerebrovascular disease, autoimmune disease, diabetes, Raynaud's disease, and life-threatening allergy (eg, anaphylaxis).

Table 5: Summary of Trial Design and Patient Demographics for Clinical Trials in Migraine Prevention

Study Name	Trial design	Dosage, route of administration and duration of study	Study subjects (n)[a]	Mean age (Range)	Sex
PROMISE 1	Parallel group, double-blind, placebo-controlled global trial Efficacy and safety in episodic[b] migraine prevention	30 mg, 100 mg, or 300 mg Intravenous infusion 24 weeks double-blind treatment period [a]	Total = 888 Placebo = 222 30 mg = 219 100 mg = 223 300 mg = 224	40 years (18 to 71)	Female: 84% Male: 16%
PROMISE 2	Parallel group, double-blind, placebo-controlled global trial Efficacy and safety in chronic[c] migraine prevention	100 mg or 300 mg Intravenous infusion 12 weeks double-blind treatment period [b]	Total = 1072 Placebo = 366 100 mg = 356 300 mg = 350	41 years (18 to 65)	Female: 88% Male: 12%

[a] The total duration of the study was 56 weeks, including a 48-week placebo-controlled treatment period followed by a safety follow-up after the last infusion at week 36.
[b] The total duration of the study was 32 weeks, including a 24-week placebo-controlled treatment period followed by a safety follow-up after the last infusion at week 12.

14.2 Study Results

Episodic Migraine
PROMISE 1 was a parallel group, double-blind, placebo-controlled global trial to evaluate the efficacy and safety of VYEPTI for the preventive treatment of episodic migraine (defined as ≥4 and ≤14 headache days of which at least 4 had to be migraine days during the 28-day screening period) in adults. A total of 888 patients were randomized (1:1:1:1) to received placebo (N=222), 30 mg eptinezumab (N=223), 100 mg eptinezumab (N=221), or 300 mg eptinezumab (N=222) every 12 weeks for 48 weeks (4 infusions). Patients were allowed to use concurrent acute migraine or headache medications, including migraine-specific medications (e.g., triptans, ergotamine derivatives), during the trial. Regular use (greater than 7 days per month) of other treatments for the prevention of migraine was not allowed. Overall, there were 856 subjects (96.4%) with at least 1 acute concomitant headache medication and 41 subjects (4.6%) with at least 1 prophylactic headache medication.

Headache information was captured daily throughout study participation using the electronic headache diary device. The primary efficacy endpoint was the change from baseline in mean monthly migraine days (MMD) over Weeks 1-12. The key secondary endpoints included migraine responder rates defined as the proportion of patients achieving the specified percent reduction in migraine days ≥ 75% over Weeks 1-4 and 1-12.

Patients had a mean age of 40 years (range: 18 to 71 years), 84% were female, and 84% were White. The mean migraine frequency at baseline was 8.6 migraine days per month and was similar across treatment groups.

The results of the study are presented in Table 6.

Table 6: Primary and Key Secondary Efficacy Endpoint Results in PROMISE 1 (Episodic Migraine)

	VYEPTI 100 mg N=221	VYEPTI 300 mg N=222	Placebo N=222
Reduction in Monthly Migraine Days (MMD) – Weeks 1-12[b]			
Baseline[a]	8.7	8.6	8.4
Mean Change from baseline	-3.9	-4.3	-3.2
Difference from placebo	-0.7	-1.1	
$CI_{95\%}$	(-1.3, -0.1)	(-1.7, -0.5)	
p-value vs placebo	0.0182	0.0001	
≥ 75% MMD responders – Weeks 1-4[c]			
Responders	30.8%	31.5%	20.3%
Difference from placebo	10.5%	11.3%	
p-value vs placebo	0.0112	0.0066	

[a] Baseline was the average over the 28-day screening period prior to receiving treatment
[b] The change from baseline in MMDs (Week 1-12) was analysed using ANCOVA with baseline MMDs as covariate and treatment as a fixed effect.
[c] For the 75% responders, eptinezumab was compared to placebo using the Cochran Mantel-Haenszel test, stratified by baseline MMDs (≤9 or >9).
Note: Type 1 error was controlled for all endpoints.

Chronic Migraine

PROMISE 2 was a parallel group, double-blind, placebo-controlled global trial to evaluate the efficacy and safety of VYEPTI for the preventive treatment of chronic migraine (defined as ≥ 15 to ≤ 26 headache days, of which ≥ 8 were assessed as migraine days) in adults. A total of 1,072 patients were randomized and received placebo (N=366), 100 mg eptinezumab (N=356), or 300 mg eptinezumab (N=350) every 12 weeks for 24 weeks (2 infusions). During the trial, patients were allowed to use an established stable regimen (except for onabotulinumtoxinA) of acute or preventive medication for migraine or headache. Patients using opioids or butalbital containing products > 4 days/month were excluded.

The primary efficacy endpoint was the change from baseline in mean monthly migraine days (MMD) over Weeks 1-12. The key secondary endpoints included the proportion of patients with 50% or greater and 75% or greater reductions from baseline in monthly migraine days over Weeks 1-12.

Patients had a mean 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 16.1 migraine days per month and was similar across treatment groups.

The results of the study are presented in Table 7.

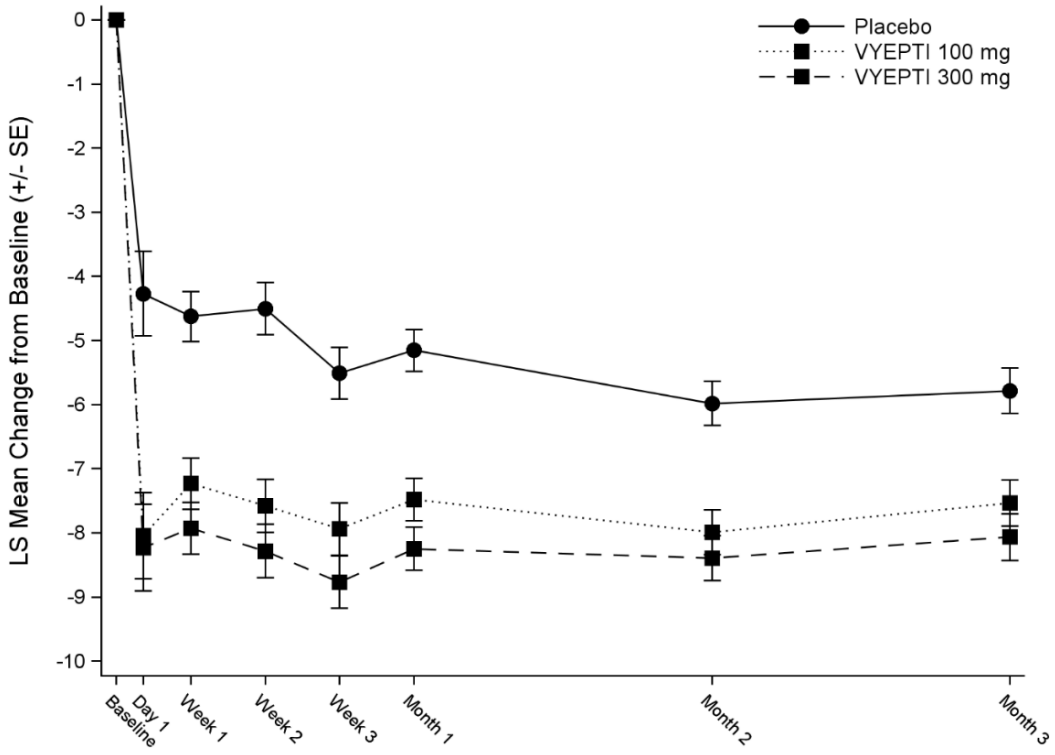
Table 7: Primary and Key Secondary Efficacy Endpoint Results in PROMISE 2 (Chronic Migraine)

	VYEPTI 100 mg N=356	VYEPTI 300 mg N=350	Placebo N=366
Reduction in Monthly Migraine Days (MMD) – Weeks 1-12[b]			
Baseline[a]	16.1	16.1	16.2
Mean Change from baseline	-7.7	-8.2	-5.6
Difference from placebo	-2.0	-2.6	
$CI_{95\%}$	(-2.9, -1.2)	(-3.5, -1.7)	
p-value vs placebo	< 0.0001	< 0.0001	
≥ 75% MMD responders – Weeks 1-12[c]			
Responders	26.7%	33.1%	15.0%
Difference from placebo	11.7%	18.1%	
p-value vs placebo	0.0001	< 0.0001	
≥ 50% MMD responders – Weeks 1-12[c]			
Responders	57.6%	61.4%	39.3%
Difference from placebo	18.2%	22.1%	
p-value vs placebo	< 0.0001	< 0.0001	

[a] Baseline was the average over the 28-day screening period prior to receiving treatment
[b] The change from baseline in MMDs (Week 1-12) was analysed using ANCOVA with baseline MMDs as covariate and treatment and prophylactic medication use (Yes/No) as fixed effects.
[c] For the 75% and 50% responders, eptinezumab was compared to placebo using the Cochran-Mantel-Haenszel test, stratified by baseline MMDs (<17 or ≥17) and prophylactic medication use (Yes/No).
Note: Type 1 error was controlled for all endpoints.

The results over Weeks 1-12, following one infusion of VYEPTI treatment are presented as change from baseline in mean MMDs (Figure 1). For both doses of VYEPTI, patients had greater mean decreases from baseline in MMDs at all timepoints through Week 12, compared to placebo-treated patients.

Figure 1: Mean Change from Baseline of MMDs, Day 1 After Infusion, and Weeks 1-12, PROMISE 2



A total of 431 patients (40%) with a dual diagnosis of chronic migraine and medication overuse headache (overuse of triptans, ergotamine, or combination analgesics > 10 days/month, or acetaminophen, acetylsalicylic acid, or non-steroidal anti-inflammatory drugs ≥ 15 days/month) were included in the study (eptinezumab 300 mg n=147, eptinezumab 100 mg n=139, and placebo n=145). The treatment difference observed between VYEPTI 100 mg and placebo and between VYEPTI 300 mg and placebo for the reduction of MMD in these patients were -3.0 days and -3.2 days, respectively.

15 NON-CLINICAL TOXICOLOGY

General toxicology

Eptinezumab was assessed for general toxicity in a 6-month repeat-dose toxicity study in cynomolgus monkeys. In that study, groups of male and female cynomolgus monkeys (n=3/sex/group) were administered 0 (vehicle only), 20, 50 or 150 mg/kg (10-, 43-, or 123-times greater than the maximum recommended human dose [MRHD] based on AUC) by IV bolus injection every two weeks for 6 months. A cohort (n=2/sex/group) was administered the same treatment and maintained as a recovery group for an additional 3 months following the main study. One low-dose female died shortly after administration of the sixth dose on study day 71. This death is considered a result of an ADA-mediated anaphylactic response. The no-observed-adverse-effect-level (NOAEL) was identified as the highest dose tested (150 mg/kg/dose).

Carcinogenicity
Non-clinical studies have not been conducted to evaluate the carcinogenic potential of eptinezumab.

Genotoxicity
Non-clinical studies have not been conducted to evaluate the genotoxic potential of eptinezumab.

Reproductive and Developmental Toxicology
In the fertility study, male and female rats were administered eptinezumab at doses of 0 (vehicle only), 75, or 150 mg/kg by IV injection once weekly during the pre-mating, mating, and gestation period (up to gestation day [GD] 4). No eptinezumab-related toxicity or effects on fertility and reproductive performance were observed. One female death was reported at a dose of 150 mg/kg from undetermined causes. The NOAEL was determined to be 150 mg/kg/dose (60-times greater than the human exposure based on body surface area).

In two embryo-fetal development studies, pregnant rats and rabbits administered eptinezumab at doses of 0 (vehicle only), 75, or 150 mg/kg by IV injection once weekly during the period of organogenesis (GD 6 to 18 in rats and GD 7 to 20 in rabbits). No maternal toxicity was reported. No fetal toxicity or teratogenicity were observed. The NOAEL was determined to be 150 mg/kg/dose (36- and 33-times greater than the MRHD based on C_{max} for the rat and rabbit studies, respectively).

In the extended pre- and postnatal development study, pregnant rats were administered eptinezumab at doses of 0 (vehicle only), 75, or 150 mg/kg by IV injection once every 6 days from GD 6 until lactation day 20. No overt maternal toxicity was reported; however, one F0 female from the high-dose group died from undetermined causes. *In utero* exposure to eptinezumab did not affect F1 male and female development, sexual maturation, fertility, or reproductive performance. The NOAEL was determined to be 150 mg/kg/dose (60-times greater than the human exposure based on body surface area).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrVYEPTI®

(Eptinezumab for injection, solution for intravenous infusion)

Read this carefully before you start taking **VYEPTI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VYEPTI**.

What is VYEPTI used for?

VYEPTI is a medicine used to prevent migraine in adults who have at least 4 migraine days per month.

How does VYEPTI work?

VYEPTI contains the active ingredient eptinezumab, which belongs to a group of substances called monoclonal antibodies. Eptinezumab blocks the activity of a protein called calcitonin gene-related peptide (CGRP). Increases in CGRP levels in the blood have been linked to migraine.

What are the ingredients in VYEPTI?

Medicinal ingredients: eptinezumab
Non-medicinal ingredients: L-histidine, L-histidine monohydrochloride, polysorbate 80, sorbitol and water for injection.

VYEPTI comes in the following dosage forms:

1 mL solution containing 100 mg of eptinezumab (100 mg/mL) in a single-use vial for intravenous infusion.

Do not use VYEPTI if:

- **you are allergic to eptinezumab or any of the other ingredients of this medicine** (*see* **What are the ingredients in VYEPTI?** *above*)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VYEPTI. Talk about any health conditions or problems you may have, including:

- heart disease
- severe liver disease
- severe kidney disease
- alcohol/drug abuse
- severe mental disorders

Other warnings you should know about:

Children and adolescents

VYEPTI should not be given to children under 18 years old. The use of VYEPTI has **not** been studied in children.

Pregnancy and breast-feeding
VYEPTI has **not** been studied in pregnant women.
Ask your doctor for advice before receiving this medicine, if you:

- are pregnant or think you may be pregnant
- are planning to have a baby
- are breast-feeding or planning to breastfeed

Your doctor will help you decide if VYEPTI is right for you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take VYEPTI:

VYEPTI should only be given by a doctor or nurse.

- VYEPTI is given by an intravenous infusion (through a needle placed in a vein in the arm, hand, or through a central line). The infusion lasts about 30 minutes.

Usual dose:
The recommended dose is 100 mg VYEPTI every 12 weeks. Some patients may benefit from a dosage of 300 mg every 12 weeks.

Before starting the treatment, your doctor will determine the amount of VYEPTI required.

Overdose:

If you think you have been given too much VYEPTI, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, contact your healthcare professional immediately for instructions.

What are possible side effects from using VYEPTI?
The following are not all possible side effects you may feel when taking VYEPTI. If you experience any side effects not listed here, contact your healthcare professional.

Common (≥ 1 in 100 and < 1 in 10)

- Nasopharyngitis (stuffy nose and sore throat)
- Allergic reaction (rash, swelling, itching, hives, itchy throat or tightness, difficulty breathing and wheezing.)

Call your healthcare professional or get emergency medical help right away if you think you are having a severe allergic reaction.

Other side effects can include infusion site reactions such as redness, swelling, or pain.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
VYEPTI will be stored by healthcare professionals at the hospital or clinic:

- Store in original package to protect from light.
- Store in a refrigerator (2°C – 8°C).
- Do **not** freeze or shake.

Keep out of reach and sight of children.

If you want more information about VYEPTI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website < https://www.canada.ca/en/health-canada.html>; the manufacturer's website www.lundbeck.com/ca/en, or by calling 1-800-586-2325

This leaflet was prepared by Lundbeck Canada Inc., Saint-Laurent, QC, H4S 0A9

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