Portrait SmPC INDONESIA eptinezumab 100mg/mL concentrate for solution for infusion

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VYEPTI®(eptinezumab) concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg eptinezumab in 1mL.Eptinezumab is a humanised monoclonal immunoglobulin G1 (IgG1) antibody.

For the full list of excipients, see section 3.2

3. PHARMACEUTICAL PARTICULARS

3.1 Pharmaceutical form

Concentrate for solution for infusion.

The concentrate for solution for infusion is clear to slightly opalescent, colourless to brownish-yellow.

3.2 List of excipients

Sorbitol

L-histidine

L-Histidine hydrochloride monohydrate

Polysorbate 80

Water for Injection

3.3 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, except those mentioned in section 3.7.

3.4 Shelf life

36 months

Following dilution, the VYEPTI solution for infusion (VYEPTI and 0.9% Sodium Chloride for Injection) must be infused within 8 hours (see Section 3.7).

3.5 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Keep the vial in the outer carton in order to protect from light.

Do not freeze or shake.

Following dilution, the VYEPTI solution for infusion (VYEPTI and 0.9% Sodium Chloride for Injection) may be stored at room temperature or refrigerated at 2 to 8°C.

3.6 Nature and contents of container

Type I glass vial with chlorobutyl rubber stopper. The vial stopper is made without natural rubber latex.

Each Carton contains one vial.

3.7 Special precautions for disposal and other handling

The product requires dilution prior to administration. The dilution should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution for infusion.

The product contains no preservative and is intended for single use only and any unused product should be disposed.

Prior to dilution, the product (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 solution for infusion as described below. No other IV diluents or volumes may be used to prepare the VYEPTI solution for infusion.

Gently invert the VYEPTI solution for infusion to mix completely. Do not shake.

Following dilution, VYEPTI solution for infusion must be infused within 8 hours. During this time, VYEPTI solution for infusion may be stored at room temperature or refrigerated at 2 to 8°C. If stored at 2 to 8°C, allow the VYEPTI solution for infusion to warm to room temperature prior to infusion. DO NOT FREEZE.

<u>100 mg dose:</u>

To prepare the VYEPTI solution for infusion, withdraw 1.0 mL of VYEPTI from one 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

<u>300 mg dose:</u>

To prepare the VYEPTI solution for infusion, withdraw 1.0 mL of VYEPTI from 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.

<u>Infusion administration instructions</u>

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.

Infuse VYEPTI 100 mg or 300 mg as prescribed, following dilution of the vial content in a 100 mL bag of 0.9% Sodium Chloride for Injection, over approximately 30 minutes. 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.

Do not administer VYEPTI as a bolus injection.

No other medications should be administered through the infusion set or mixed with VYEPTI.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VYEPTI is indicated for the preventive treatment of migraine in adults.

4.2 Posology and method of administration

As for other infusion treatments, VYEPTI treatment should be initiated and supervised by a healthcare professional.

Posology

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 5.1).

Special Populations

Elderly (aged 65 years and over)

Although patients aged up to 75 years were included in one study, 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.

Paediatric population

The safety and efficacy of eptinezumab in children below the age of 18 years has not yet been established. Currently no data are available.

Method of administration

Eptinezumab is for intravenous infusion only after dilution.

For instructions on dilution of the medicinal product prior to administration, see section 3.7.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 3.2.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Cardiovascular risk

Patients with a history of cardiovascular disease (e.g. hypertension, ischemic heart disease) were excluded from clinical studies (see section 5.1). No safety data are available in these patients.

Serious hypersensitivity

Serious hypersensitivity reactions, including anaphylactic reactions, have been reported and may develop within minutes of the infusion. Most hypersensitivity reactions occurred during infusion and were not serious (see section 4.8). If a serious hypersensitivity reaction occurs, administration of VYEPTI should be discontinued immediately and appropriate therapy initiated.

Excipients

This medicinal product contains 40.5 mg of sorbitol in each mL

4.5 Interaction with other medicinal products and other forms of interactions

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.

In healthy subjects, 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 alter the pharmacokinetics of eptinezumab or sumatriptan.

Interactions with other drugs have not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of eptinezumab in pregnant women. Animal studies with eptinezumab do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Human IgG is known to cross the placental barrier; therefore, eptinezumab may be transmitted from the mother to the developing fetus.

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

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 effects on the breastfed infant.

Fertility

The effect of eptinezumab on human fertility has not been evaluated. Animal studies with eptinezumab showed no impact on female and male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

VYEPTI is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

A total of over 2000 patients (more than 1,600 patient years) have been treated with VYEPTI in clinical studies. 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 (two doses), 991 patients were exposed for 48 weeks (four doses), and 101 patients were exposed for up to two years (eight doses). In the placebo-controlled clinical studies (PROMISE 1 and PROMISE 2), 1372 patients received at least one dose of VYEPTI (including 579 patients receiving at least one dose of VYEPTI 100 mg and 574 patients receiving at least one dose of VYEPTI 300 mg), and 588 patients received placebo. Approximately 86% were female, 89% were white, and the mean age was 40.4 years at study entry.

Patients with a history of cardiovascular disease, neurological disease, cerebrovascular disease, morbid obesity and diabetes were excluded from clinical studies.

The most common adverse reactions in the placebo-controlled clinical studies (PROMISE 1 and PROMISE 2) for the preventive treatment of migraine were nasopharyngitis and hypersensitivity (see below). Most hypersensitivity reactions occurred during infusion and were not serious.

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 PROMISE 1 and PROMISE 2.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification. Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100; rare (≥1/10,000 to <1/1,000; very rare (<1/10,000).

Table 1: List of Adverse Reactions in Clinical Studies and Post-marketing reports

System Organ Class	Adverse Reaction Preferred Term	Frequency Category
Infections and Infestations	Nasopharyngitis	Common
Immune system disorders	Hypersensitivity reactions	Common
	Anaphylactic reaction[1]	Rare

[1] Not reported in PROMISE 1 and PROMISE 2, but reported in other studies and in the post-marketing setting.

Description of selected adverse reactions

Nasopharyngitis

Approximately 8% of patients on 300 mg, 6% of patients on 100 mg and 6% of patients on placebo in PROMISE 1 and PROMISE 2 experienced nasopharyngitis. Nasopharyngitis was most frequent after the first dose of eptinezumab at any dose. The incidence decreased with subsequent doses and remained fairly steady thereafter.

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylactic reactions, have been reported and may develop within minutes of the infusion (see section 4.4). The reported anaphylactic reactions have included symptoms of hypotension and respiratory difficulties, and have led to discontinuation of VYEPTI. Other hypersensitivity reactions, including angioedema, urticaria, flushing, rash and pruritus, were reported in 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.

Immunogenicity

In placebo-controlled pivotal clinical studies, PROMISE 1 and PROMISE 2, 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, and thereafter showed a steady decline even after subsequent dosing every 12 weeks. The incidence of antibodies with

neutralizing potential across both studies was 8.3% (48/579) and 6.1% (35/574) for the 100 mg and 300 mg treatment groups, respectively.

A long-term open label repeat dose study, PREVAIL, in 128 patients with chronic migraine consisted of a primary and secondary treatment phase in which up to eight IV infusions of VYEPTI 300 mg were administered over an 84-week period (one infusion every 12 weeks). Overall 119 patients completed the primary treatment phase (4 infusions, from baseline up to 48 weeks) and 101 patients completed the secondary treatment phase (8 infusions; from baseline up to 96 weeks). Anti-drug antibodies (ADA) developed in 18% (23/128) of patients with an overall incidence of antibodies with neutralizing potential of 7% (9/128). 5.3% patients were ADA positive at week 48, 4% were ADA positive at week 72, and all patients, except one patient lost to follow-up, were ADA negative at week 104 (the last assessment in the study).

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

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

There has been no experience of overdose with VYEPTI. 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, the patient should be treated symptomatically, and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not yet assigned.

ATC code: N02CD05

Mechanism of action

Eptinezumab is a humanized immunoglobulin G1 (IgG1) antibody that binds to α- and β- forms of human calcitonin gene-related peptide (CGRP) ligand with low picomolar affinity (4 and 3 pM K_D, respectively). This, in combination with the 100% bioavailability following an IV administration, translates into fast blockage of the biological effects of circulating CGRP in humans. As a result, eptinezumab prevents the activation of the CGRP receptors and hence the downstream cascade of physiological events linked to initiation, frequency and severity of migraine attacks.

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

Pharmacodynamic effects

Pharmacodynamic activity characterized by inhibition of α-CGRP-mediated neurogenic vasodilation induced by topical capsaicin relative to baseline was evaluated following single or multiple administrations of eptinezumab in human volunteers. Mean neurogenic induced vasodilation was reduced by 41% following intravenous 100 mg eptinezumab administration compared to an increase of 12% for placebo on the day following treatment. For up to 12 weeks, the reduction persisted ranging from 20% to 50% for 100 mg eptinezumab while placebo ranged from a 20% increase to 0.20% reduction during the same period.

Clinical efficacy and safety

VYEPTI was evaluated for the preventive treatment of migraine in two pivotal placebo-controlled studies: PROMISE 1 was conducted in patients with episodic migraine (n=888) and PROMISE 2 in patients with chronic migraine (n=1072). In PROMISE 1 episodic migraine was defined as ≥4 and ≤14 headache days of which at least 4 had to be migraine days in each 28-day period in the 3 months prior to screening. In PROMISE 2 chronic migraine was defined as ≥ 15 to ≤ 26 headache days, of which ≥ 8 were assessed as migraine days. VYEPTI was administered by intravenous infusion every 12 weeks in both studies. Enrolled patients had a history of migraine (with or without aura) of at least 12 months, according to the International Classification of Headache Disorders (ICHD-II or III) diagnostic criteria. Patients over 75 years and patients with a history of cardiovascular disease, neurological disease, cerebrovascular disease, and diabetes were excluded.

The long-term safety of VYEPTI following repeated dosing for up to 2 years was further evaluated in patients with chronic migraine in an open-label study, PREVAIL, (n=128).

PROMISE 1: Episodic Migraine

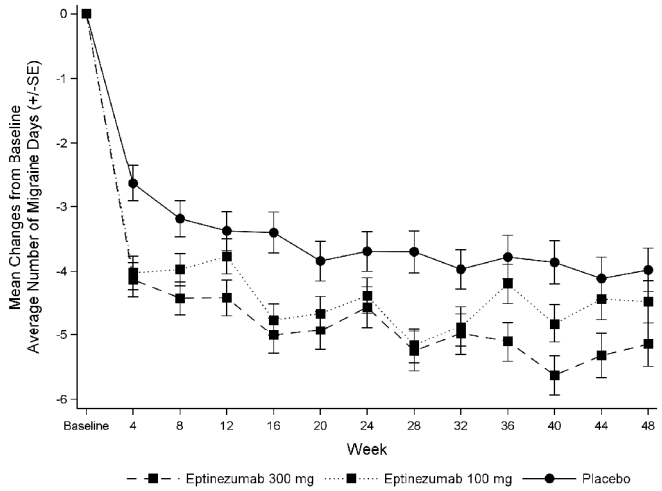
PROMISE 1 was a parallel group, double-blind, placebo-controlled global study to evaluate the efficacy and safety of VYEPTI for the preventive treatment of episodic migraine in adults. 665 patients were randomized to placebo (N=222), 100 mg eptinezumab (N=221), or 300 mg eptinezumab (N=222) every 12 weeks for 48 weeks (4 infusions). Patients were allowed concurrent acute migraine or headache medications, including migraine-specific medications (i.e., triptans, ergotamine derivatives), during the study. Regular use (greater than 7 days per month) of other treatments for the prevention of migraine was not allowed.

The primary efficacy endpoint was the change from baseline in mean monthly migraine days (MMD) over Weeks 1-12. The key secondary endpoints included ≥ 50% and ≥ 75% migraine responder rates defined as the proportion of patients achieving at least the specified percent reduction in migraine days over Weeks 1-12, ≥ 75% migraine responder rate over Weeks 1-4, and the percentage of patients with a migraine on the day after the first dosing (Day 1).

Patients had a mean age of 40 years (range: 18 to 71 years), 84% were women, and 84% were white. The mean number of migraine days per month at baseline was 8.6 and the rate of patients with a migraine on a given day was 30.7% during the screening period; both were similar across treatment groups.

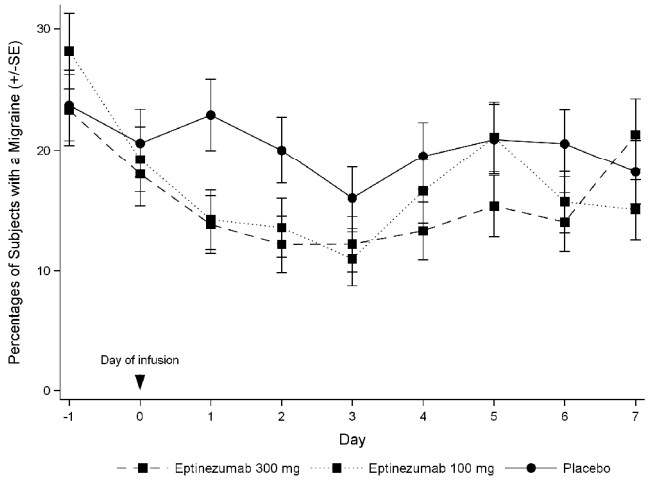
The 4-week results over Weeks 1-48, following four quarterly infusions of VYEPTI treatment are presented as changes from baseline in mean MMD (Figure 1). Both VYEPTI 100 mg and 300 mg treatment groups demonstrated statistically significant and clinically meaningful greater improvements from baseline to week 1-12 compared to placebo on mean MMD. For both doses of VYEPTI, a greater mean decrease in MMDs compared to placebo was sustained for all timepoints through Week 48.

Figure 1 Mean Changes from Baseline in Mean Monthly Migraine Days over Time in PROMISE 1 – Weeks 1-48



The daily results over the first week after the initial infusion of VYEPTI treatment are presented as percentages of patients with a migraine (Figure 2).For both doses of VYEPTI the preventive treatment benefit over placebo was observed as early as Day 1 post-infusion.

Figure 2: Percentages of Patients with a Migraine from Day -1 (Day Prior to Infusion) to Day 7 in PROMISE 1 – Days 1-7



VYEPTI treatment demonstrated statistically significant and clinically meaningful improvements for primary and key secondary efficacy endpoints, as summarized in Table 2.

Table 2: 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
Monthly Migraine Days (MMD) – Weeks 1-12			
Baseline	8.7	8.6	8.4
Mean Change	-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			
Responders	30.8%	31.5%	20.3%
Difference from placebo	10.5%	11.3%	
p-value vs placebo	0.0112	0.0066	
≥ 75% MMD responders – Weeks 1-12			
Responders	22.2%	29.7%	16.2%
Difference from placebo	6.0%	13.5%	
p-value vs placebo	0.1126	0.0007	
≥ 50% MMD responders – Weeks 1-12			
Responders	49.8%	56.3%	37.4%
Difference from placebo	12.4%	18.9%	
p-value vs placebo	0.0085	0.0001	
Percent of Patients with a Migraine on the Day After Dosing			
Migraine during the Baseline Period[a]	31.0%	30.8%	29.8%
Day 1	14.8%	13.9%	22.5%
p-value vs placebo	0.0312	0.0159	

[a] A baseline was the average over the 28-day screening period prior to receiving treatment

Additional secondary efficacy endpoints in PROMISE 1 substantiated results from the key efficacy endpoints. In line with the ≥ 50% and ≥ 75% migraine responder rates, 100% migraine responder rates (average of 4-week means across Weeks 1-12) were higher for both doses of VYEPTI compared to placebo (100 mg and 300 mg: 11.4% and 16.8% vs placebo: 9.1%).

PROMISE 2: Chronic Migraine

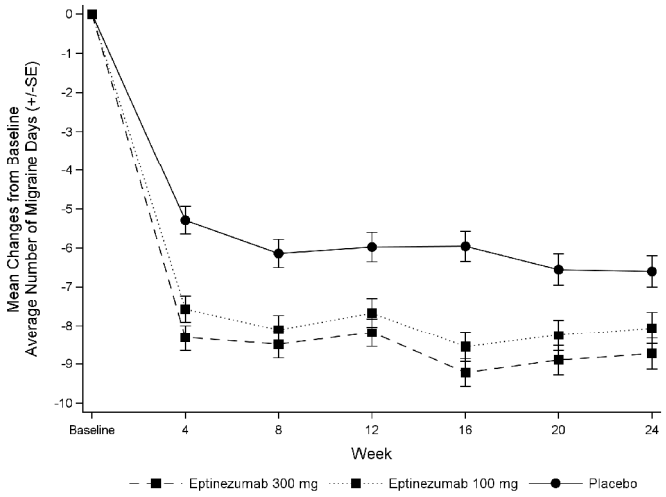
PROMISE 2 was a parallel group, double-blind, placebo-controlled global study to evaluate the efficacy and safety of VYEPTI for the preventive treatment of chronic migraine in adults. A total of 1,072 patients were randomized and received placebo (N=366), 100 mg eptinezumab (N=356), or 300 mg eptinezumab (N=350) every 12 weeks for 24 weeks (2 infusions). During the study, patients were allowed to use acute or preventive medication for migraine or headache on an established stable regimen (except for onabotulinumtoxinA). Patients with a dual diagnosis of chronic migraine and medication overuse headache (associated with the 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 population. Patients taking opioids or butalbital containing products > 4 days/month were excluded.

The primary efficacy endpoint was the change from baseline in mean MMD over Weeks 1-12. The key secondary endpoints included ≥ 50% and ≥ 75% migraine responder rates defined as the proportion of patients achieving the specified percent reduction in migraine days over Weeks 1-12, ≥ 75% migraine responder rate over Weeks 1-4, the percentage of patients with a migraine on the day after dosing, the reduction in migraine prevalence from baseline to Week 4, the change from baseline in the total score on the Headache Impact Test (HIT-6) at Week 12 (300 mg dose only), and the change from baseline in acute monthly migraine medication days, mean over Weeks 1-12 (300 mg dose only). The HIT-6 is a self-administered questionnaire assessing the impact of headache on the functional status of patients with migraine. Interpretation of the impact of migraine on daily function by total score is as follows: 60-78 = Severe; 56-59 = Substantial, 50-55 = Some, and 36-49 = little to none.

Patients had a mean age of 41 years (range: 18 to 65 years), 88% were women, and 91% were white. Forty-one percent of patients were taking concomitant preventive medication for migraine. The mean number of migraine days per month at baseline was 16.1 and the rate of patients with a migraine on a given day was 57.6% during the screening period; both were similar across treatment groups.

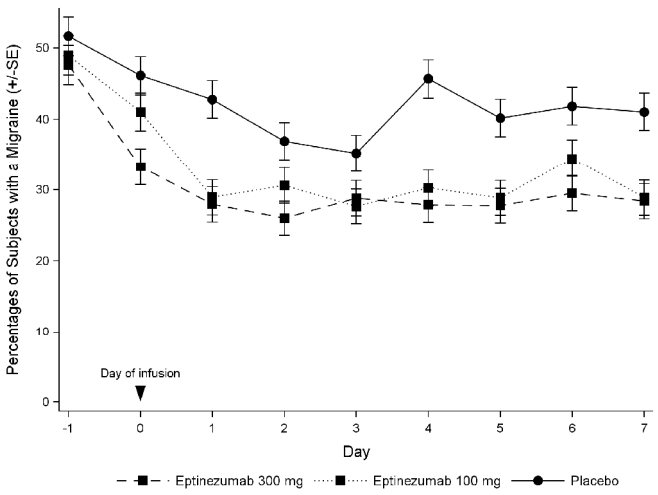
The monthly results over Weeks 1-24, following two quarterly infusions of VYEPTI treatment are presented as changes from baseline in mean MMD (Figure 3). Both VYEPTI 100 mg and 300 mg treatment groups demonstrated statistically significant and clinically meaningful greater improvements from baseline to week 1-12 compared to placebo on mean MMD. For both doses of VYEPTI, a greater mean decrease in MMDs compared to placebo was sustained for all timepoints through to Week 24.

Figure 3: Mean Changes from Baseline in Mean Monthly Migraine Days in PROMISE 2 - Weeks 1-24



The daily results over the first week after the initial infusion of VYEPTI treatment are presented as percentages of patients with a migraine (Figure 4). A preventive treatment benefit over placebo for both doses of VYEPTI was observed as early as Day 1 post-infusion.

Figure 4: Percentages of Patients with a Migraine from Day -1 (Day Prior to Infusion) to Day in PROMISE 2 – Days 1-7



Eptinezumab treatment demonstrated statistically significant and clinically meaningful improvements for key efficacy endpoints as summarized in Table 3.

Table 3: 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
Monthly Migraine Days (MMD) – Weeks 1-12			
Baseline	16.1	16.1	16.2
Mean Change	-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 1-4			
Responders	30.9%	36.9%	15.6%
Difference from placebo	15.3%	21.3%	
p-value vs placebo	< 0.0001	< 0.0001	
≥ 75% MMD responders – Weeks 1-12			
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			
Responders	57.6%	61.4%	39.3%
Difference from placebo	18.2%	22.1%	
p-value vs placebo	< 0.0001	< 0.0001	
Percent of Patients with a Migraine on the Day After Dosing			
Migraine during the Baseline Period[a]	57.5%	57.4%	58.0%
Day 1	28.6%	27.8%	42.3%
p-value vs placebo	< 0.0001	< 0.001	
Reduction in Migraine Prevalence[b] – Weeks 1-4			
Mean Change	-27.1%	-29.8%	-18.8%
Difference from placebo	-8.3%	-11.0%	
$CI_{95\%}$	(-11.5%, -5.1%)	(-14.2%, -7.8%)	
p-value vs placebo	< 0.0001	< 0.0001	
HIT-6 Score – Week 12[c]			
Baseline	65.0	65.1	64.8
Mean Change	-6.2	-7.3	-4.5
Difference from placebo	-1.7	-2.9	
$CI_{95\%}$	(-2.8, -0.7)	(-3.9, -1.8)	

p-value vs placebo	0.0010	< 0.0001	
Days per month with Acute Medication Use – Weeks 1-12[a,c]			
Baseline	6.6	6.7	6.2
Mean Change	-3.3	-3.5	-1.9
Difference from placebo	-1.2	-1.4	
$CI_{95\%}$	(-1.7, -0.7)	(-1.9, -0.9)	
p-value vs placebo	< 0.0001	< 0.0001	

[a] A baseline was the average over the 28-day screening period prior to receiving treatment
[b] Migraine prevalence: The average percent of patients with a migraine on any given day during baseline and the equivalent average rates over weeks 1, 2, 3, and 4
[c] The endpoint for the 100 mg dose was not a pre-specified key secondary endpoint.

Additional secondary efficacy endpoints in PROMISE 2 substantiated results from the key efficacy endpoints. In line with the ≥ 50% and ≥ 75% migraine responder rates, 100% migraine responder rates (average of 4-week means across Weeks 1-12) were higher for both doses of VYEPTI compared to placebo (100 mg and 300mg: 10.8% and 15.1% vs placebo: 5.1%).

Patients with medication overuse headache (MOH), other than those taking opioids or butalbital > 4 days/month, were enrolled in PROMISE 2: at baseline, 40.2% of the patients had MOH. In patients with chronic migraine, similar reductions in MMD (Mean for Weeks 1-12) were observed in patients with and without MOH at baseline. The mean change from baseline in MMD (Weeks 1-12) for the patients with MOH was for 300 mg: -8.6, 100 mg: -8.4, placebo: -5.4 and for patients without MOH was 300 mg: -8.1, 100 mg: -7.4, placebo:-6.1.The mean difference to placebo in change from baseline in MMD (Weeks 1-12) for the patients with MOH was (300 mg: -3.2 [95% CI: -4.75; -1.70], 100 mg: -3.0 [-4.52; -1.49]) and for patients without MOH was (300 mg: -2.4 [-3.59; -1.12], 100 mg: -1.5 [-2.70; -0.31]).

PREVAIL: Long-term study

VYEPTI 300 mg was administered every 12 weeks by IV infusion in patients with chronic migraine in an open-label study for up to 2 years, with the primary objective of further evaluating the long-term safety following repeated doses of VYEPTI. Secondary objectives included characterization of the PK and immunogenicity profiles for VYEPTI (section 4.8) and evaluation of the therapeutic effect of VYEPTI on several patient reported outcomes relating to migraine and quality of life including the Headache Impact Test (HIT-6). Patients had a mean age of 41.5 years (range: 18 to 65 years), 85% were women, and 95% were white. Thirty-six percent of patients were taking concomitant preventive medication for migraine. The mean number of migraine days per 28-day period in the 3 months preceding screening was 14.1 days. There were 128 enrolled and treated patients in this study. In total, 100 patients (78.1%) completed the study (Week 104). Overall, the results of this open-label clinical study demonstrated that VYEPTI 300 mg administered by IV infusions every 12 weeks for the preventive treatment of migraine was associated with a sustained and clinically meaningful therapeutic effect, demonstrated by reductions in headache impact, improvements in measures of health-related quality of life, and overall improvement of change in migraine over 2 years of treatment in adults with chronic migraine.

Patients were severely impacted at Baseline with a mean total HIT-6 score of 65 which decreased through Week 104 to a score of 56 ($p<0.0001$).

Patients were severely disabled at Baseline with a mean total score on MIDAS of 56.8 which decreased through Week 104 to a score of 36.7 ($p<0.0001$).

Patients showed clinically meaningful improvements in the physical (PCS) and mental component summary (MCS) scores of the SF-36v2: the mean change from Baseline at Week

104 in MCS (baseline 51.3) was 3 (p=0.0045), and in PCS (baseline 46.7) was 4.3 (p<0.0001).

The safety profile was consistent with the safety profiles observed in randomized, placebo-controlled studies with VYEPTI.

5.2 Pharmacokinetic properties

As eptinezumab is administered intravenously, it is 100% bioavailable. Eptinezumab exhibits linear pharmacokinetics and exposure increases proportionally with doses from 1 to 1000 mg. Steady-state is attained after the first-dose during a once every 12 weeks dosing schedule. Median time to maximum concentration (C_{max}) is 30 minutes (end-of-infusion), and the average terminal elimination half-life is 27 days. The mean accumulation ratios based on C_{max} and $AUC_{0\text{-}tau}$ are 1.08 and 1.15, respectively.

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

Biotransformation

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

Elimination

Eptinezumab apparent clearance was 0.15 L/day, and the terminal elimination half-life was approximately 27 days.

Special populations

The pharmacokinetics of eptinezumab were not affected by age, gender, or race based on population pharmacokinetics. Therefore, no dose adjustment is needed.

Renal or Hepatic Impairment

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 of integrated data from the VYEPTI clinical studies did not reveal any differences in patients with renal or hepatic impairment that would require dose adjustment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, or toxicity to reproduction and development.

Safety pharmacology and general toxicology

Safety pharmacology and general toxicity assessments after intravenous (IV) administration of eptinezumab once every 2 weeks for 6 months in cynomolgus monkeys identified the no-

observed-adverse-effect-level (NOAEL) as the highest dose tested (150 mg/kg/dose). This supports a 103-fold or 123-fold safety margin, respectively, by Cmax or AUC for the highest dose (300 mg) administered by IV infusion every 12 weeks in humans.

Genotoxicity and Carcinogenesis

Genotoxicity testing was not warranted for eptinezumab due to the mechanism of action and the biological nature of a monoclonal antibody.

No carcinogenicity studies have been performed with eptinezumab.

Reproductive and Developmental Toxicology

Eptinezumab administered by weekly IV at doses of 0, 75 or 150 mg/kg/dose showed no adverse effects on male or female fertility (rats), embryofetal development (rats and rabbits), postnatal survival, growth, or development during the pre- and postweaning period, including behavioral or reproductive performance (rats).

For all studies, the NOAEL was the highest dose tested (150 mg/kg) which is 35-fold higher than the highest recommended human dose, based on body weight.

6. MARKETING AUTHORISATION HOLDER

Manufactured and packaged for:

H. Lundbeck A/S, Ottiliavej 9,

2500 Valby, Denmark

By Vetter Pharma-Fertigung

GmbH & Co. KG,

Mooswiesen 2, Ravensburg

Baden-Wuerttemberg

88214, Germany

HARUS DENGAN RESEP DOKTER

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

Reg. No.

Registered by:

PT Pyridam Farma, Tbk
Jakarta - Indonesia