# SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions

## 1 NAME OF THE MEDICINAL PRODUCT

VYEPTI 100 mg concentrate for solution for infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VYEPTI 100 mg concentrate for solution for infusion
Each vial of concentrate contains 100 mg eptinezumab per mL.

Eptinezumab is a humanized monoclonal antibody produced in Pichia pastoris yeast cells.

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 6.1.

## 3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (Sterile concentrate).

The concentrate for solution for infusion is clear to slightly opalescent, colourless to brownish-yellow with a pH of 5.5-6.1 and osmolality of 290-350 mOsm/kg.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

## 4.2 Posology and method of administration

The treatment should be initiated by a healthcare professional experienced in the diagnosis and treatment of migraine. The infusion of VYEPTI 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).

The need for dose escalation should be assessed within 12 weeks after initiation of the treatment. When switching dosage, the first dose of the new regimen should be given on the next scheduled dosing date.

Overall benefit and continuation of treatment should be assessed 6 months after initiation of the treatment. Any further decision to continue the treatment should be made on an individual patient basis.

*Special Populations*
*Elderly (aged 65 years and over)*
There is limited data available for the use of VYEPTI in patients ≥65 years of age. No dose adjustment is required in the elderly patients as the pharmacokinetics of eptinezumab were not affected by age.

*Renal impairment/hepatic impairment*
No dose adjustment is required in patients with renal impairment or hepatic impairment (see section 5.2).

*Paediatric population*
The safety and efficacy of VYEPTI in children aged 6 to 18 years has not yet been established. Currently no data are available.
There is no relevant use of VYEPTI in children below the age of 6 years for the prophylaxis of migraine.

Method of administration
VYEPTI is for intravenous use only after dilution.

For instructions on dilution of the medicinal product prior to administration, see section 6.6.

Following dilution, infuse VYEPTI over approximately 30 minutes.

The treating healthcare professional should observe or monitor patients during and after the infusion in accordance with normal clinical practice.

Do not administer VYEPTI as a bolus injection.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 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 medicinal product should be clearly recorded.

Patients with cardiovascular, neurological or psychiatric diseases
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. Limited safety data are available in patients with cardiovascular risk factors such as diabetes, circulatory diseases and hyperlipidaemia.

Patients with a history of neurological diseases or patients with psychiatric conditions that were uncontrolled and/or untreated were excluded from the clinical studies. Limited 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. If the hypersensitivity reaction is not serious, continuation of further treatment with VYEPTI is up to the discretion of the treating physician, taking into account the benefit-risk for the individual patient.

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.

## 4.5 Interaction with other medicinal products and other forms of interaction

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.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
There is 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.

As a precautionary measure, it is preferable to avoid the use of VYEPTI during pregnancy.

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 during the first few days after birth, which is decreasing to low concentrations soon afterward; consequently, a risk to the breastfed infant cannot be excluded during this short period. Afterwards, use of eptinezumab could be considered during breast-feeding only if clinically needed.

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 has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile
Over 2 000 patients have been treated with VYEPTI in clinical studies. Of these, approximately 1 000 patients were exposed for 48 weeks (four doses). The most common adverse reactions were nasopharyngitis and hypersensitivity. 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.

Tabulated list of adverse reactions

Adverse reactions from clinical trials and post-marketing experience (table 1) are classified by MedDRA system organ classification and frequency. 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**

| **System organ class** | **Adverse reaction preferred term** | **Frequency category** |
|---|---|---|
| Infections and infestations | Nasopharyngitis | Common |
| Immune system disorders | Hypersensitivity reactions | Common |
| | Anaphylactic reaction[1] | Uncommon |
| *General disorders and administration site conditions* | Infusion-related reaction | Common |
| | Fatigue | Common |

[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 VYEPTI at any dose. The incidence decreased notably with subsequent doses and remained fairly steady thereafter.

*Hypersensitivity and infusion-related 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.

Other symptoms reported in association with eptinezumab infusion include respiratory symptoms (nasal congestion, rhinorrhea, throat irritation, cough, sneezing, dyspnea) and fatigue (see below). Most of these events were non-serious and transient in nature.

*Fatigue*

Approximately 3% of patients on eptinezumab and 2% of patients on placebo in the placebo-controlled clinical trials experienced fatigue. Fatigue was most frequent on the day of the first infusion. Following the first week and with

subsequent infusions, fatigue was reported in lower incidences and the incidences were comparable to placebo.

*Immunogenicity*
In the 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, 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 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, PREVAIL (up to 96 weeks of treatment with 300 mg VYEPTI every 12 weeks), 18% (23/128) of patients developed anti-eptinezumab antibodies with an overall incidence of neutralizing antibodies 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).

In the clinical studies, 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.

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:
**United Kingdom**
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

### 4.9 Overdose

Doses up to 1 000 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: analgesics, calcitonin gene-related peptide (CGRP) antagonists, ATC code: N02CD05.

Mechanism of action

Eptinezumab is a recombinant 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 Kd, respectively). Eptinezumab prevents the activation of the CGRP receptors and hence the downstream cascade of physiological events linked to initiation of migraine attacks.

Eptinezumab inhibits α and β- CGRP-mediated neurogenic inflammation and vasodilation.

Eptinezumab is highly selective (>100 000-fold *vs* related neuropeptides amylin, calcitonin, adrenomedullin and intermedin).

Clinical efficacy and safety

VYEPTI (eptinezumab) 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). 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.

*PROMISE 1: episodic migraine*

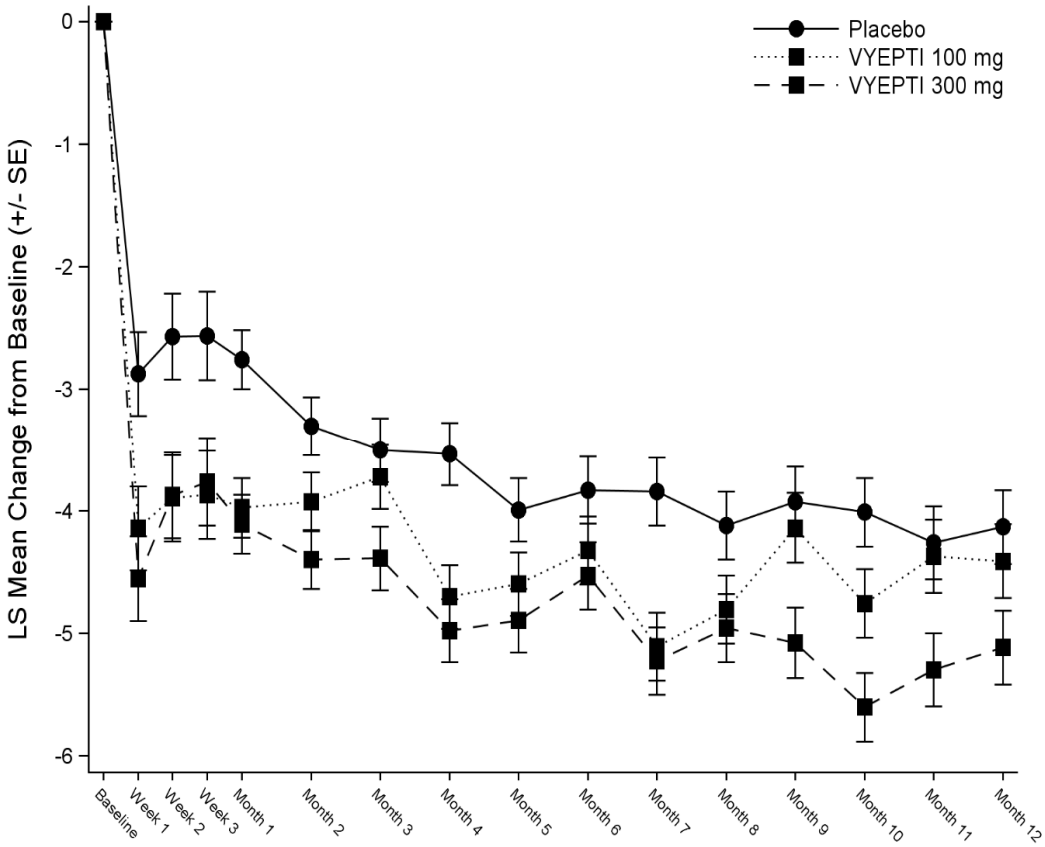
PROMISE 1 was a parallel group, double-blind, placebo-controlled study to evaluate the efficacy and safety of VYEPTI for the preventive treatment of episodic migraine in adults. 665 patients were randomized to receive placebo (N=222), 100 mg eptinezumab (N=221), or 300 mg eptinezumab (N=222) every 12 weeks for 48 weeks (4 infusions). 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 and confirmed during baseline period. 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. At baseline 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 31%; both were similar across treatment groups.

Reduction in mean monthly migraine days from placebo for both doses was observed from the first day after administration.

**Figure 1 Mean changes from baseline of monthly migraine days in PROMISE 1**




LS = least square; VYEPTI = eptinezumab

At each timepoint, an ANCOVA including treatment and prophylactic medication use as factors and baseline migraine days as a continuous covariate was used to estimate the mean change from baseline.

**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 | |

*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). Chronic migraine was defined as ≥ 15 to ≤26 headache days, of which ≥8 were assessed as migraine days in the 3 months prior to screening and confirmed during the 28-day screening period. During the study, patients were allowed acute or preventive medication for migraine or headache on an established stable regimen (except for onabotulinumtoxinA).

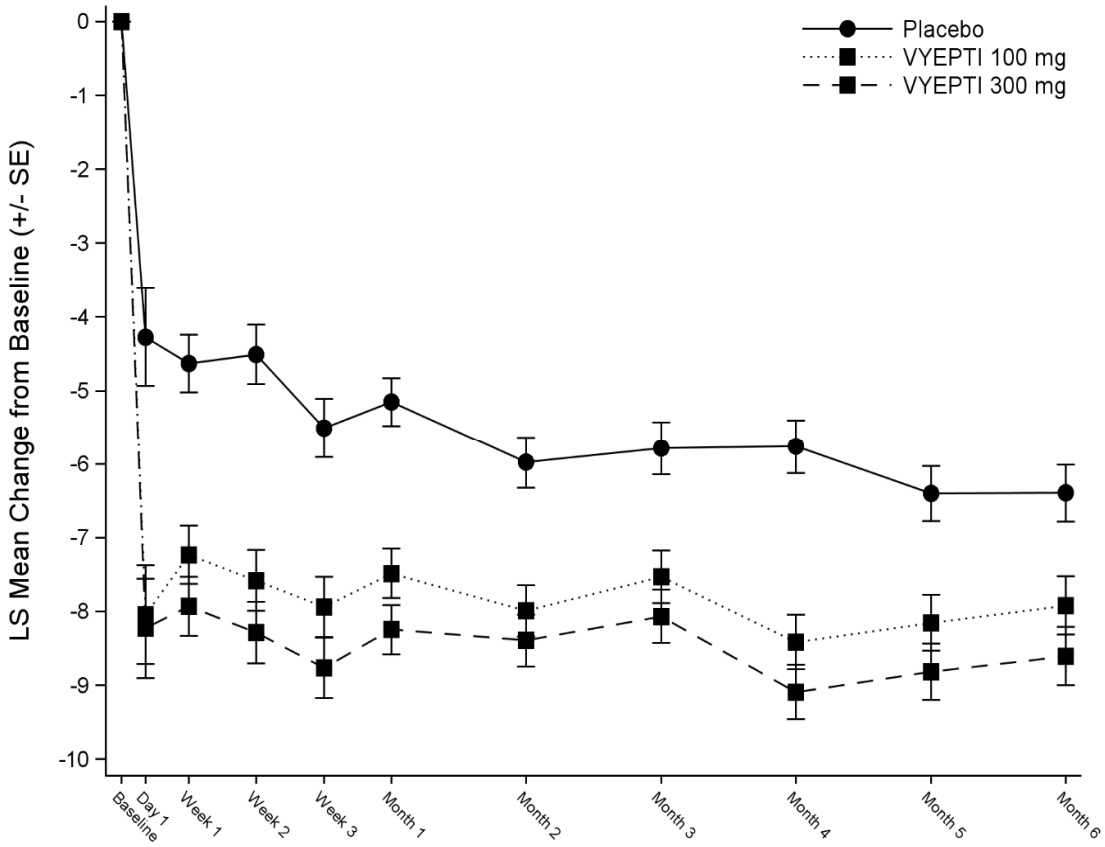
A total of 431 patients (40%) with a dual diagnosis of chronic migraine and medication overuse headache (associated with the overuse of triptans, ergotamine, or combination analgesics >10 days/month, or acetaminophen, acetylsalicylic acid, or non-steroidal anti-inflammatory drugs ≥15 days/month) confirmed during screening period were included in the study population.

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).
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. At baseline 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%; both were similar across treatment groups.

Reduction in mean monthly migraine days from placebo for both doses was observed from the first day after administration.

***Figure 2:*** ***Mean changes from baseline of monthly migraine days in PROMISE 2***




LS = least square; VYEPTI = eptinezumab
At each timepoint, an ANCOVA including treatment as a factor and baseline migraine days as a continuous covariate was used to estimate the mean change from baseline.

**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 | |
| HIT-6 score – Week 12[a] | | | |
| 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,b] | | | |
| 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] The endpoint for the 100 mg dose was not a pre-specified key secondary endpoint.
[b] A baseline was the average over the 28-day screening period prior to receiving treatment

*Patients diagnosed with medication overuse headache*

In the 431 (40%) patients diagnosed with medication-overuse headache (MOH) in PROMISE-2, the mean change from baseline in MMD (weeks 1-12) was for VYEPTI 100 mg -8.4 days, VYEPTI 300 mg -8.6 days, and placebo -5.4 days (mean difference to placebo of -3.0 days and -3.2 days for 100 mg and 300 mg, respectively).

DELIVER: Prior migraine preventive treatment failures

VYEPTI has been evaluated in an efficacy and safety study (DELIVER) in patients with episodic (n=484) and chronic (n=405) migraine and documented failure of two to four classes of prior migraine preventive treatment, which included a 24-week double-blind, placebo-controlled treatment period and a 48-week long term extension period.

The study showed that VYEPTI treatment led to a mean reduction in monthly migraine days (MMD) over Week 1-12: -4.8 in VYEPTI 100 mg group and -5.3 in the VYEPTI 300 mg group, compared to -2.1 in the placebo group, corresponding to a difference from placebo of -2.7 days (95% CI: -3.4 to -2.0) and -3.2 days (95% CI: -3.9 to -2.5), respectively.

The study also showed that ≥50% reduction in MMD over Week 1-12 was achieved for 42% in the VYEPTI 100 mg group and for 50% in the VYEPTI 300 mg group, compared to 13% in the placebo group. The ≥75% reduction in MMD over Week 1-12 was achieved in 16% in the VYEPTI 100 mg group and 19% in the VYEPTI 300 mg group, compared to 2% of subjects in the placebo group.

The demonstrated efficacy in the placebo-controlled treatment period was sustained for up to 72 weeks of VYEPTI treatment in the extension period.

The safety data was consistent with the safety profile of VYEPTI as described in section 4.8.

RELIEF: Initiation of preventive treatment during a migraine attack

VYEPTI has been evaluated in an efficacy and safety study (RELIEF) in patients with 4 to 15 migraine days per month (n=480). The patients received VYEPTI or placebo within 1-6 hours after the onset of a moderate to severe migraine attack.

The study supports that treatment with VYEPTI when initiated during a moderate to severe migraine attack, demonstrates statistically significantly shortened time to headache pain freedom ($p<0.001$; median time 4 hours vs 9 hours) and symptom resolution for the most bothersome symptom ($p<0.001$; median time 2 hours vs 3 hours) compared to placebo in patients eligible for migraine-preventive treatment. More migraine patients treated with VYEPTI also experienced headache pain freedom (24% vs 12%) and absence of most bothersome symptoms (56% vs 36%) at 2 hours compared to placebo ($p<0.001$), and within the first 24 hours after infusion, fewer patients required acute rescue medication after VYEPTI treatment vs placebo ($p<0.001$).

The safety data was consistent with the safety profile of VYEPTI as described in section 4.8.

*PREVAIL: long-term study*
VYEPTI 300 mg was administered every 12 weeks by IV infusion for up to 96 weeks in 128 patients with chronic migraine. The primary objective was to evaluate 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, 95% were white, and 36% took 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. In total, 100 patients (78.1%) completed the study (week 104). Patients were severely impacted at baseline with a mean total HIT-6 of 65. The mean change from baseline through week 104 was -9.7 ($p<0.0001$). The safety profile was consistent with the safety profiles observed in the randomized, placebo-controlled studies, and a sustained effect on patient-relevant outcomes was observed for up to 96 weeks.

Paediatric population
The licensing authority has deferred the obligation to submit the results of studies with VYEPTI in one or more subset of the paediatric population in the preventive treatment of migraine (see section 4.2 for information on paediatric use)

## 5.2 Pharmacokinetic properties

As VYEPTI is administered intravenously, it is 100% bioavailable. Eptinezumab exhibits linear pharmacokinetics and exposure increases proportionally with doses from 10 to 1 000 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 litres.

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
A population pharmacokinetic analysis including 2 123 subjects explored the effect of age, gender, ethnicity and body weight on the pharmacokinetics of eptinezumab. Relative to a 70 kg subject, steady state exposure of eptinezumab in a 190 kg subject was up to 52% lower, whereas is would be up to 50% higher in a 39 kg subject. However, from the exposure-response evaluation, there was no effect of body weight on the clinical efficacy. No dose adjustment is required based on body weight. The pharmacokinetics of eptinezumab were not affected by age (18-71), 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. *No data for patients with severe renal impairment are available.*

### 5.3 Preclinical safety data

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

Genotoxicity and Carcinogenesis
As eptinezumab is unlikely to interact directly with DNA or other chromosomal material, evaluations for potential genotoxicity were considered unnecessary and not performed.

As no carcinogenicity risk has been identified by extensive evaluation of the literature related to inhibition of CGRP and as no eptinezumab-related proliferative findings were observed in long term studies in monkeys, carcinogenicity testing was considered unnecessary and not performed.

## 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sorbitol (E420)
L-histidine
L-histidine hydrochloride monohydrate
Polysorbate 80
Water for injections

## 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

## 6.3 Shelf life

3 years.

Following dilution, the VYEPTI solution for infusion (VYEPTI and 0.9% sodium chloride for injection) must be infused within 8 hours (see section 6.6).

## 6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze or shake.

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

If removed from the refrigerator, Vyepti must be used within 7 days when stored in original carton at room temperature (up to 25°C), or discarded. If it is stored at a higher temperature or for a longer period it must be discarded.

Following dilution, the VYEPTI solution for infusion (VYEPTI and 0.9% sodium chloride for injection) may be stored at room temperature (below 25°C) or refrigerated at 2°C - 8°C. Following dilution, VYEPTI solution for infusion must be infused within 8 hours.

## 6.5 Nature and contents of container

4 mL type I glass vial with chlorobutyl rubber stopper. The vial stopper is made without natural rubber latex.

Each carton contains one vial.

## 6.6 Special precautions for disposal and other handling

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

Prior to dilution, the medicinal product (concentrate in the vials) should be inspected visually; do not use if the concentrate 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 sodium chloride 9 mg/mL (0.9%) solution for injection should be used to prepare the VYEPTI solution for infusion as described below. No other intravenous diluents or volume 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 (below 25°C) or refrigerated at 2°C - 8°C. If stored at 2°C - 8°C, allow the VYEPTI solution for infusion to warm to room temperature prior to infusion. DO NOT FREEZE.

<u>VYEPTI 100 mg dose</u>
To prepare the VYEPTI solution for infusion, withdraw 1.0 mL of VYEPTI from one single-use 100 mg 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>VYEPTI 300 mg dose</u>
To prepare the VYEPTI solution for infusion, withdraw 1.0 mL of VYEPTI from 3 single-use 100 mg vials or 3.0 mL of VYEPTI from one single-use 300 mg vial 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 medicinal products should be inspected visually for particulate matter and discoloration prior to administration. Do not use if the liquid contains visible particulate matter or is cloudy or discoloured.

Infuse VYEPTI 100 mg dose or VYEPTI 300 mg dose 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.

## 7 MARKETING AUTHORISATION HOLDER

Lundbeck Limited
Iveco House, Station Road,
Watford, Hertfordshire, WD17 1ET,
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

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## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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## 10 DATE OF REVISION OF THE TEXT

21/11/2024