

ANNEX I

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.

VYEPTI 300 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.

VYEPTI 300 mg concentrate for solution for infusion

Each vial of concentrate contains 300 mg eptinezumab per 3 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

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 breast-fed 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 2000 patients have been treated with VYEPTI in clinical studies. Of these, approximately 1000 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10000$ to $< 1/1000$); very rare ($< 1/10000$).

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 [the national reporting system](#) listed in [Appendix V](#).

4.9 Overdose

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: 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 K_d, 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

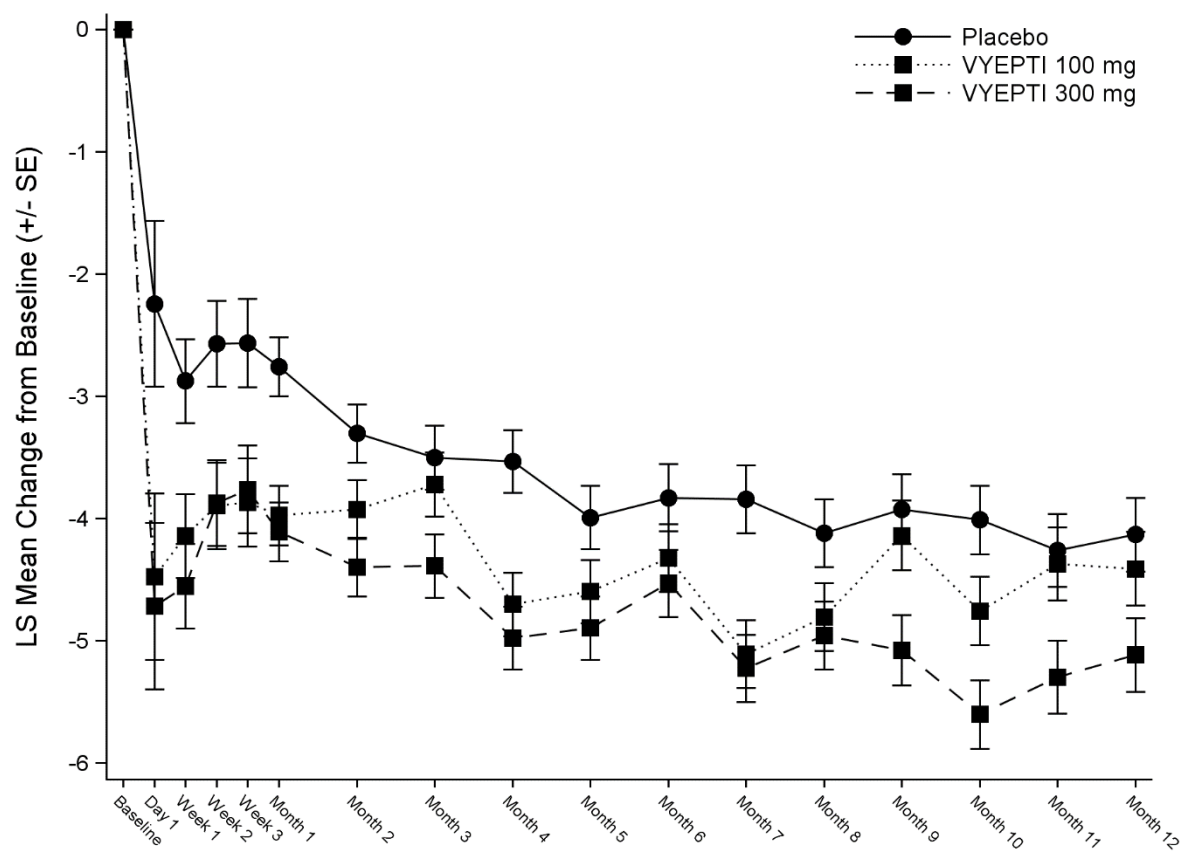
PROMISE 1 was a parallel group, double-blind, placebo-controlled study to evaluate the efficacy and safety of VYEPTI for the preventive treatment of episodic migraine in adults. 665 patients were randomized to receive placebo (N=222), 100 mg eptinezumab (N=221), or 300 mg eptinezumab (N=222) every 12 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 $\geq 50\%$ and $\geq 75\%$ migraine responder rates defined as the proportion of patients achieving at least the specified percent reduction in migraine days over weeks 1-12, $\geq 75\%$ 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

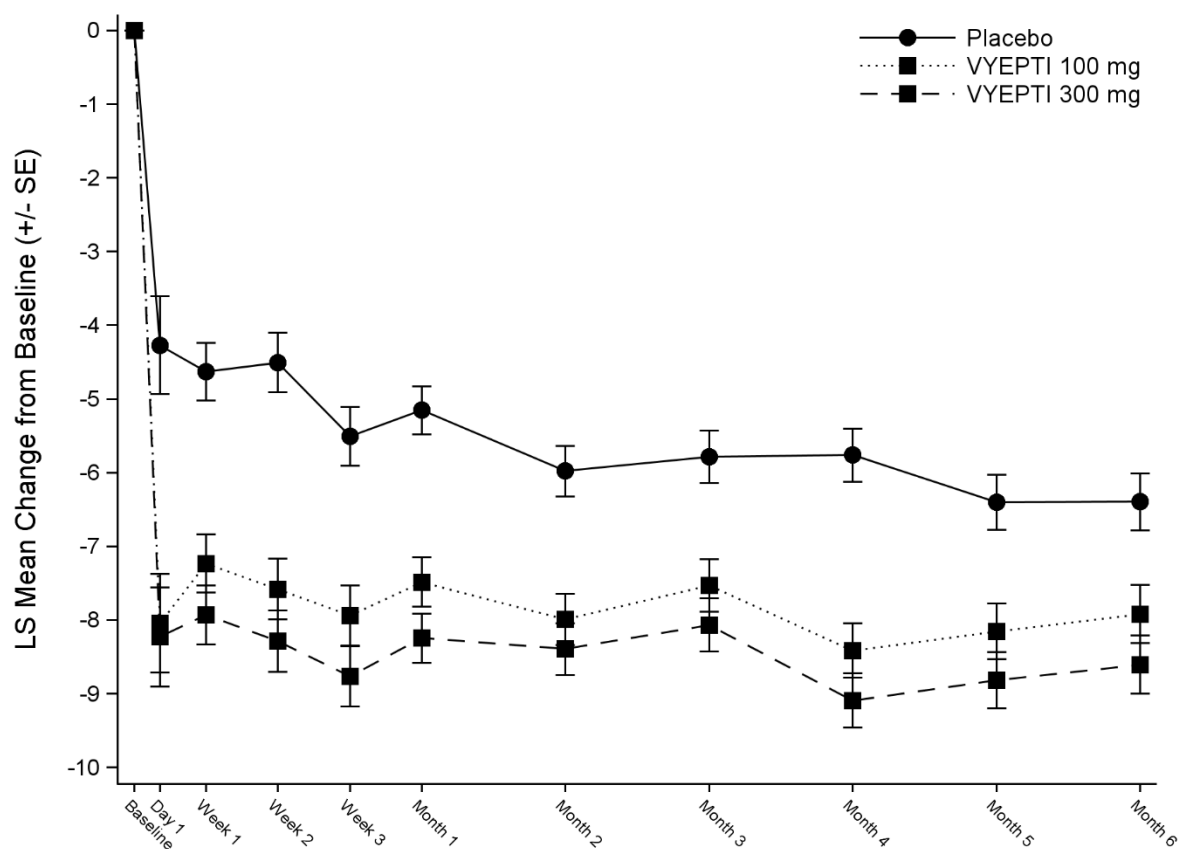
PROMISE 2 was a parallel group, double-blind, placebo-controlled global study to evaluate the efficacy and safety of VYEPTI for the preventive treatment of chronic migraine in adults. A total of 1,072 patients were randomized and received placebo (N=366), 100 mg eptinezumab (N=356), or 300 mg eptinezumab (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 $\geq 50\%$ and $\geq 75\%$ migraine responder rates defined as the proportion of patients achieving the specified percent reduction in migraine days over weeks 1-12, $\geq 75\%$ 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)	
<i>p</i> -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%	
<i>p</i> -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%	
<i>p</i> -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%	
<i>p</i> -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)	
<i>p</i> -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)	
<i>p</i> -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).

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 European Medicines Agency 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 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 $AUC_{0-\tau}$ 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 (V_c) 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 it 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 2 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.

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.

VYEPTI 100 mg concentrate for solution for infusion

VYEPTI is available in pack sizes of 1 and 3 vial(s) for single-use.

VYEPTI 300 mg concentrate for solution for infusion

VYEPTI is available in pack size of 1 vial for single-use.

Not all pack sizes may be marketed.

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.

VYEPTI 100 mg dose

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

VYEPTI 300 mg dose

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.

Infusion administration instructions

Parenteral medicinal 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 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

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1599/001
EU/1/21/1599/002
EU/1/21/1599/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24. January 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S)
AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING
AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE
AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

Name and address of the manufacturer(s) responsible for batch release

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this medicinal product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

VYEPTI 100 mg concentrate for solution for infusion
eptinezumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of concentrate contains 100 mg eptinezumab per mL.

3. LIST OF EXCIPIENTS

Excipients: sorbitol, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80 and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Sterile concentrate

1 vial

3 vials

1 mL

3x1 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after dilution.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze or shake.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1599/001
EU/1/21/1599/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS VIAL
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1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

VYEPTI 100 mg sterile concentrate
eptinezumab
IV use after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

VYEPTI 300 mg concentrate for solution for infusion
eptinezumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of concentrate contains 300 mg eptinezumab per 3 mL.

3. LIST OF EXCIPIENTS

Excipients: sorbitol, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80 and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Sterile concentrate
1 vial
3 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after dilution.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze or shake.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1599/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS VIAL
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

VYEPTI 300 mg sterile concentrate
eptinezumab
IV use after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

3 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

VYEPTI 100 mg concentrate for solution for infusion **VYEPTI 300 mg concentrate for solution for infusion** eptinezumab

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What VYEPTI is and what it is used for
2. What you need to know before you are given VYEPTI
3. How to use VYEPTI
4. Possible side effects
5. How to store VYEPTI
6. Contents of the pack and other information

1. What VYEPTI is and what it is used for

VYEPTI contains the active substance eptinezumab, which blocks the activity of calcitonin gene-related peptide (CGRP), a naturally occurring substance in the body. People with migraine may have increased levels of this substance.

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

VYEPTI can reduce the number of days with migraine and improve your quality of life. You may feel the preventive effect starting the day after receiving this medicine.

2. What you need to know before you are given VYEPTI

Do not use VYEPTI

- if you are allergic to eptinezumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or nurse before being given VYEPTI if you have disease affecting the heart and blood circulation.

VYEPTI can cause serious allergic reactions. These reactions can develop quickly even while the medicine is being given. Tell your doctor immediately if you get any symptoms of an allergic reaction, such as:

- breathing difficulty
- a fast or weak pulse or a sudden drop in blood pressure which makes you feel dizzy or lightheaded

- swelling of the lips or tongue
- severe itching of the skin or rash while you receive VYEPTI, or afterwards

Children and adolescents

VYEPTI is not recommended for children or adolescents under 18 years because it has not been studied in this age group.

Other medicines and VYEPTI

Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine.

It is preferable to avoid the use of VYEPTI during pregnancy as the effects of this medicine in pregnant women are not known.

It is not known if VYEPTI passes into breast milk. Your doctor will help you decide if you should stop breast-feeding or stop VYEPTI treatment. If you are breast-feeding or are planning to breast-feed, talk to your doctor before being treated with VYEPTI. You and your doctor should decide if you should breast-feed and be treated with VYEPTI.

Driving and using machines

VYEPTI has no or negligible effect on the ability to drive or use machines.

VYEPTI contains sorbitol

Sorbitol is a source of fructose. If you have hereditary fructose intolerance (HFI), a rare genetic disorder, you must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.

You must tell your doctor before receiving this medicine if you have HFI.

3. How to use VYEPTI

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

VYEPTI is given as a drip (infusion) into a vein. The infusion lasts about 30 minutes. VYEPTI will be given to you by a healthcare professional, who prepares the infusion before giving it to you. During and after the infusion the healthcare professional will observe you in accordance with normal clinical practice for signs of an allergic reaction.

The recommended dose is 100 mg given every 12 weeks. Some patients may benefit from a dose of 300 mg given every 12 weeks. Your doctor will decide the right dose for you and how long you should continue to be treated.

If you use more VYEPTI than you should

Because the medicine will be given to you by a healthcare professional, it is unlikely you will receive too much VYEPTI. Inform your doctor if you think this has happened.

If you forget to use VYEPTI

If a dose is missed, your doctor will decide when the next dose should be given.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor or nurse immediately if you notice any of the following side effects – you may need urgent medical treatment:

Common: may affect up to 1 in 10 people:

- **allergic reactions and other reactions due to the infusion**
Reactions can develop quickly during infusion. Symptoms of allergic reactions are:
 - breathing difficulties
 - fast or weak pulse
 - sudden drop in blood pressure making you feel dizzy or lightheaded
 - swelling of the lips or tongue
 - severe skin itching, rashSerious allergic reactions are uncommon (may affect up to 1 in 100 people).

Other symptoms that may occur due to the infusion include respiratory symptoms (such as blocked or runny nose, throat irritation, cough, sneezing, shortness of breath) and feeling tired. These symptoms are usually non-serious and of short duration.

Other side effects can occur with following frequency:

Common: may affect up to 1 in 10 people:

- stuffy nose
- sore throat
- fatigue

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store VYEPTI

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

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 kept at room temperature (below 25°C) in the original carton and used within 2 days, or else discarded. Do not put VYEPTI back in the refrigerator once it has been removed.

After dilution, the solution may be stored at room temperature (below 25°C) or in a refrigerator at 2°C - 8°C. The diluted solution for infusion must be given within 8 hours.

Do not use this medicine if you notice that the solution contains visible particles or is cloudy or discolored.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What VYEPTI contains

- The active substance is eptinezumab.
- Each vial of 100 mg concentrate contains 100 mg of eptinezumab per mL.
- Each vial of 300 mg concentrate contains 300 mg of eptinezumab per 3 mL.
- The other ingredients are sorbitol (E420), L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80 and water for injections.

What VYEPTI looks like and contents of the pack

VYEPTI concentrate for solution for infusion is clear to slightly milky, colourless to brownish-yellow. Each vial contains concentrate in a clear glass vial with a rubber stopper, aluminium seal and plastic flip-off cap.

VYEPTI 100 mg concentrate is available in pack sizes of 1 and 3 vial(s) for single-use.
VYEPTI 300 mg concentrate is available in pack size of 1 vial for single-use.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

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The following information is intended for healthcare professionals only:

Instructions for dilution and administration

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.

- VYEPTI 100 mg dose

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

- VYEPTI 300 mg dose

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.

Infusion administration instructions

Parenteral medicinal 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 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.