*Date:* 2 December 2021
Swissmedic, Swiss Agency for Therapeutic Products

# *Swiss Public Assessment Report*

# Vyepti

**International non-proprietary name:** eptinezumab
**Pharmaceutical form:** concentrate for solution for infusion
**Dosage strength:** 100 mg/ml
**Route(s) of administration:** intravenous use
**Marketing Authorisation Holder:** Lundbeck (Schweiz) AG
**Marketing Authorisation No.:** 67995
**Decision and Decision date:** approved on 11 October 2021

**Note:**

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.



Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

## About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

## About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.



Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Table of contents





Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

# 1 Terms, Definitions, Abbreviations

| | |
|---|---|
| ADA | Anti-drug antibody |
| ADME | Absorption, Distribution, Metabolism, Elimination |
| ALT | Alanine aminotransferase |
| API | Active pharmaceutical ingredient |
| ATC | Anatomical Therapeutic Chemical Classification System |
| AUC | Area under the plasma concentration-time curve |
| AUC0-24h | Area under the plasma concentration-time curve for the 24-hour dosing interval |
| CGRP | Calcitonin gene-related peptide |
| CM | Chronic migraine |
| Cmax | Maximum observed plasma/serum concentration of drug |
| Ctrough | Trough or minimum serum concentration |
| CYP | Cytochrome P450 |
| ECG | Electrocardiogram |
| e.g. | For example |
| EM | Episodic migraine |
| ERA | Environmental Risk Assessment |
| Fc | Fragment crystallisable |
| GLP | Good Laboratory Practice |
| ICH | International Council for Harmonisation |
| Ig | Immunoglobulin |
| INN | International Nonproprietary Name |
| LoQ | List of Questions |
| MAH | Marketing Authorisation Holder |
| Max | Maximum |
| Min | Minimum |
| MMD | Monthly migraine days |
| N/A | Not applicable |
| NO(A)EL | No Observed (Adverse) Effect Level |
| PD | Pharmacodynamics |
| PE | Polyethylene |
| PIP | Paediatric Investigation Plan (EMA) |
| PK | Pharmacokinetics |
| PopPK | Population PK |
| PSP | Pediatric Study Plan (US-FDA) |
| PVC | Polyvinyl chloride |
| RMP | Risk Management Plan |
| SAEs | Serious adverse events |
| SE-HPLC | Size-exclusion high-performance liquid chromatography |
| SwissPAR | Swiss Public Assessment Report |
| TEAEs | Treatment emergent adverse events |
| TPA | Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21) |
| TPO | Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21) |



Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

# 2 Background Information on the Procedure

## 2.1 Applicant's Request(s)

**New Active Substance status**
The applicant requested the status of a new active entity for the active substance eptinezumab of the medicinal product mentioned above.

## 2.2 Indication and Dosage

### 2.2.1 Requested Indication

Prophylactic treatment of migraine in adults, if indicated.

### 2.2.2 Approved Indication

Prophylactic treatment of migraine in adults, if indicated.

### 2.2.3 Requested Dosage

The recommended dosage is 100 mg as an intravenous infusion every 12 weeks. Some patients may benefit from a dosage of 300 mg as an intravenous infusion every 12 weeks.

### 2.2.4 Approved Dosage

(see appendix)

## 2.3 Regulatory History (Milestones)

| | |
|---|---|
| Application | 1 May 2020 |
| Formal control completed | 27 May 2020 |
| List of Questions (LoQ) | 9 September 2020 |
| Answers to LoQ | 21 December 2020 |
| Predecision | 17 March 2021 |
| Answers to Predecision | 16 May 2021 |
| Labelling corrections | 23 July 2021 |
| Answers to Labelling corrections: | 23 August 2021 |
| Final Decision | 11 October 2021 |
| Decision | approval |



Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

# 3 Medical Context

Migraine is a common neurological disorder that affects around 5% of the adult population (1-year prevalence: 8% in men, 20% in women) in western countries. It is characterised by episodic, often disabling, headache, associated with sensory (aura) and autonomic symptoms (nausea, vomiting), phonophobia and photophobia, and cognitive symptoms. Episodic migraine (EM) is defined as <15 headache days per month, although in clinical prophylactic trials a lower threshold of a minimum of 4 headache days is often chosen to reflect typical patients in need of a prophylactic treatment. Chronic migraine (CM) is defined as 15 or more headache days per month. At least 8 of these 15 or more headache days have to be typical migraine days (for the exact definition see the International Classification of Headache Disorders, 3rd edition).
There are established and approved substances for the acute treatment of migraine symptoms (such as triptans), and substances for the prevention of migraine attacks (such as beta blockers or topiramate).
Growing evidence indicates that calcitonin gene-related peptides (CGRPs) play a key role in peripheral sensitisation and associated enhanced pain, and that these peptides could be involved in migraine pathophysiology. Blocking the calcitonin gene-related peptide (CGRP) or the CGRP receptor has emerged as a possible mechanism for the prevention of migraine attacks. Amongst others, decreasing blood flow in cerebral vessels and inhibition of pain transmission in the trigeminal ganglion are discussed as possible mechanisms for these antibodies.
For several antibodies targeting the CGRP-pathway, effects in preventing migraine have been shown in clinical trials and, since 2018, three of these antibodies (erenumab, galcanezumab, fremanezumab) have been approved worldwide for the prophylaxis of episodic and chronic migraine. These substances show moderate efficacy comparable to established treatment options, combined with a rather benign safety profile. Eptinezumab is the fourth anti-CGRP antibody in this indication, but the first one with an intravenous (vs. subcutaneous) mode of administration.

# 4 Quality Aspects

## 4.1 Drug Substance

The active substance of Vyepti, eptinezumab, is a recombinant, humanised IgG1 kappa monoclonal antibody. It specifically binds to both isoforms of calcitonin gene-related peptide (α- and β-CGRP) and thereby inhibits the binding of CGRP to the CGRP receptor. Eptinezumab consists of four polypeptide chains, two identical light and two identical heavy chains. The light and heavy chain variable regions are comprised of both human and humanised rabbit sequences.
Eptinezumab has been engineered to replace the asparagine residue at position 297 (N297) with alanine, which eliminates N-linked glycosylation in the CH2 (Fc) domain of the antibody and reduces or eliminates binding to Fcγ receptors. Eptinezumab is post-transcriptionally modified by O-glycosylation (mannosylation).
Eptinezumab is produced in genetically modified yeast cells (*Pichia pastoris*) using conventional fermentation and purification process steps.

During development, the manufacturing process was transferred from the site where clinical lots were produced to the commercial manufacturing site. Validation studies at the commercial manufacturing site have demonstrated that the drug substance manufacturing process is robust and process- and product-related impurities are efficiently removed. Comparability between sites was demonstrated for lot release, extended characterisation, forced degradation studies and stability. This was supported by a Phase 1 clinical comparative pharmacokinetic study.

Extensive characterisation of the physicochemical, biological and immunological properties of eptinezumab was performed using state of the art techniques. Product- and process-related substances and impurities are adequately addressed.



Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Selected specification tests and acceptance criteria are in place to confirm the overall quality, safety, purity and potency of the eptinezumab at release and throughout the shelf life. All compendial methods are performed in accordance with the respective monograph and non-compendial methods are validated per ICH requirements.

Based on the submitted stability data, the proposed storage conditions and shelf life of the drug substance in its commercial container are considered satisfactory.

## 4.2 Drug Product

The finished drug product Vyepti is a concentrate for solution for infusion containing 100 mg/mL eptinezumab. Vyepti is a sterile, clear to slightly opalescent, colourless to brownish-yellow solution for intravenous administration. The drug product is formulated in a histidine-buffered solution containing sorbitol and polysorbate 80 and is presented as a single-use preservative-free concentrate (1 mL per vial). For intravenous administration, the solution for infusion is prepared by adding drug product, either 1.0 mL (from one vial) or 3.0 mL (1.0 mL from each of three vials), to an infusion bag (PE or PVC) containing 100 mL of sterile 0.9% saline.

The manufacturing process of the finished drug product consists of thawing, compounding, sterile filtration, aseptic filling/stoppering/sealing, inspection, assembly and labelling steps. The manufacturing process was transferred from the site where clinical lots were manufactured to the commercial manufacturing site; no changes in the unit formulation were made. Process validation studies were successfully completed at the commercial site using three commercial scale validation batches.

The release and stability specifications include relevant tests and limits, e.g. for appearance, identity, pH, extractable volume, purity/impurity tests (e.g. SE-HPLC), protein content, potency, particulate matter, sterility and bacterial endotoxins. The analytical procedures are validated in accordance with ICH guidelines.
Batch analysis data of batches manufactured for non-clinical and clinical development and for commercial production are demonstrated to be comparable. All batch release data comply with the drug product specifications that were valid at the time of batch release.

The primary container closure system consists of a 1 mL type I glass vial closed with a coated rubber stopper and sealed with an aluminium cap with a flip-off component.

The drug product is stored at 2 – 8°C. Under the proposed storage conditions a slight decrease in purity is observed, although all shelf life acceptance criteria are fulfilled at the end of the shelf life. A shelf life of 24 months has been accepted.

## 4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.
The data submitted in this application are adequate to support the conclusion that the manufacture of Vyepti is well-controlled and leads to a product that is pure and potent.



Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

## 5 Nonclinical Aspects

Regarding the marketing authorisation application of Vyepti, the Nonclinical Assessment division conducted an abridged evaluation, which was based on the FDA assessment report (approval 21 February 2020) provided by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Vyepti with the new active substance eptinezumab in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.
All excipients are well known. Impurities are considered adequately controlled.
Since eptinezumab is a protein, the risk for the environment is considered negligible.
Two studies in juvenile rats were conducted in the course of the development of Vyepti for paediatric patients. In the definitive study with weekly intravenous administration from Day 28 to Day 91 postpartum, no adverse effects on development were observed up to the high dose level of 150 mg/kg/week (30-fold the maximum recommended dose in adult patients based on body weight).



Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

# 6 Clinical and Clinical Pharmacology Aspects

## 6.1 Clinical Pharmacology

The available assessment reports and the respective product information from the US FDA were used as the basis for the clinical pharmacology evaluation. For further details concerning clinical pharmacology, see Section 8.1 of this report.

## 6.2 Dose Finding and Dose Recommendation

The randomised placebo-controlled phase 2 study 005 with approximately 600 chronic migraine patients investigated doses of 10, 30, 100 and 300 mg eptinezumab and placebo. Patients were dosed with one single infusion of the four different eptinezumab doses or placebo and were followed over 54 weeks. The primary endpoint was a 75% responder analysis in monthly migraine days over weeks 1 to 12, where a weak dose response was shown, with significant results for 100 mg and 300 mg, and non-significant results for 10 mg and 30 mg. However, other endpoints such as mean monthly migraine days showed no difference between 30 mg and 100 mg. The 30 mg dose was not further studied in the phase 3 chronic migraine trial 011. In the episodic migraine trial 006, the 30 mg dose showed a statistically significant difference vs. placebo and numerically better results compared to the 100 mg dose. While dose finding was not completely satisfactory regarding a possible 30 mg dose, the choice of 100 mg and 300 mg is generally regarded as plausible.

## 6.3 Efficacy

Two pivotal trials were submitted, one with episodic migraine patients (study 006) and one with chronic migraine patients (study 011).

*Episodic migraine*
Study 006 was a parallel group, double-blind, randomised, placebo-controlled trial. Patients were randomised (in a 1:1:1:1 ratio) to one of three dose levels of eptinezumab (30 mg, 100 mg and 300 mg) or placebo. Randomisation was stratified by migraine days during screening (≤ 9 days or > 9 days).
The total study duration was 60 weeks with 12 scheduled visits. There was a baseline period of 4 weeks to determine eligibility, followed by treatment with eptinezumab/placebo on day 0, 84 (week 12), 168 (week 24) and 252 (week 36), and a follow-up period of 20 weeks following the final dose. All four of the scheduled infusions were given 12 weeks apart, and patients kept an eDiary for recording symptoms and migraines in between infusions through week 48. Patients were allowed to use acute migraine treatment as concomitant medication, but no prophylactic treatment. The primary endpoint was the reduction in monthly migraine days (MMD) vs. baseline vs. placebo during the first 12 weeks, based on eDiary entries by patients.
In study 006, at least one treatment was received by n = 224 patients in the 30 mg group, 225 patients in the 100 mg group, 224 in the 300 mg group and 225 patients in the placebo group. The study was performed mainly in the US, accounting for 84.4% of the study population, and the remaining 15.6% were recruited in the Republic of Georgia. About 84% of the participants were white, 12% were black and the rest belonged to other races. The mean age was about 40 years, the mean time since migraine diagnosis was 17 years, around 84% were women, the number of mean monthly migraine days (MMD) at baseline was 8.6 days, the number of monthly headache days was 10, the number of monthly migraine attacks was 6.4. Around 33% of patients had migraine with aura at baseline. Discontinuation rates were about 13-17%, with a discontinuation rate due to adverse events of only 1%. Demographics and baseline disease characteristics were balanced between the treatment groups. The compliance with eDiary entries was around 85-90% during the double-blind treatment phase without relevant differences between treatment groups. The included population can be regarded as adequate for the requested indication, and comparable overall to the populations in episodic migraine studies of the other already approved CGRP antibodies. The design of the study can also be regarded as adequate.



Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

*Efficacy results in episodic migraine:*
In the primary endpoint analyses, statistically significant differences vs. placebo were reached for eptinezumab 300 mg (-1.1 MMD) and eptinezumab 100 mg (-0.69 MMD). The primary endpoint for the eptinezumab 30 mg arm was nominally significant (treatment difference -0.82 MMD) but, according to the statistical decision rule, the 30 mg treatment arm was not statistically significant. Effects for several secondary endpoints such as 50%, 75% and 100% responder differences and acute migraine medication days showed moderate and partly statistically significant differences vs. placebo. Some other secondary endpoints like “percent patients with severe intensity of migraine or migraine hours per 4 weeks” showed larger differences in favour of active treatments. Subgroup analyses for age, sex and race did not show relevant differences. Sensitivity analyses (excluding possibly unblinded patients, other analyses using different imputation methods for missing data) supported the primary analyses without relevant differences in the outcomes.

*Chronic migraine*
Study 011 was a parallel-group, double-blind, randomised, placebo-controlled trial, and patients were randomised to one of two dose levels of eptinezumab (100 mg or 300 mg) or placebo. Patients were randomised in a 1:1:1 ratio, and randomisation was stratified by baseline migraine days during screening (< 17 or ≥ 17 days), as well as prophylactic medication use during the 3 months prior to screening.
The total study duration was 36 weeks with 10 scheduled visits. There was a baseline period of 4 weeks to determine eligibility, followed by treatments on day 0 and day 84 (week 12), and a follow-up visit 20 weeks after the final dose (week 32). The scheduled infusions were given 12 weeks apart. Prophylactic headache medications were permitted, assuming that the dose had been stable for at least 3 months with no changes allowed through week 24. Endpoints and overall design were similar to study 006, with the primary endpoint being reduction in monthly migraine days (MMD) vs. baseline vs. placebo during the first 12 weeks, and secondary endpoints were similar to those in study 006.
In study 011, at least one treatment was received by n = 356 patients in the 100 mg group, 350 in the 300 mg group and 366 patients in the placebo group. The study was performed in 13 countries, with the majority of study centres and study participants (58%) in the US, 14.4% in the EU (Czech Republic, Germany, Denmark, Spain, Hungary, Italy, Slovakia, United Kingdom) and 27% in other countries (Georgia, Ukraine, Russia). 91% of the participants were white, 8% were black and the rest belonged to other races.
The mean age was about 41 years, the mean time since migraine diagnosis was 18 years, around 88% were women, the mean number of monthly migraine days (MMD) at baseline was 16, the number of monthly headache days was 20.5, the number of monthly migraine attacks was around 12, and patients used acute migraine medication at baseline on 6-7 days. Around 35% of patients had migraine with aura at baseline. Early discontinuation rates were about 6%, with a discontinuation rate due to adverse events of only 1%. Demographics and baseline disease characteristics were balanced between the treatment groups.
The included population and the study design can be regarded as adequate for the requested indication. Compliance with eDiary entries was around 90% during the double-blind treatment phase weeks 1-12 without relevant differences between treatment groups.

*Efficacy results in chronic migraine:*
In the primary endpoint analyses, statistically significant differences vs. placebo were reached for eptinezumab 300 mg (-2.6 MMD) and eptinezumab 100 mg (-2.0 MMD). Effects in several secondary endpoints such as 50%, 75% and 100% responder differences and acute migraine medication days were also statistically significant. Subgroup analyses for age and sex did not show relevant differences, while slightly lower efficacy results were noted for black patients compared to white patients. Patients without aura had higher effects compared to patients with aura, and patients without prior prophylactic treatment had higher effects compared to patients with prior prophylactic treatment. Sensitivity analyses using different imputation methods for missing data supported the primary analyses.



Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

For further details, please see the “Properties/effects” and “Clinical efficacy” sections of the information for healthcare professionals

## 6.4 Safety

A total of 2,076 patients were exposed to eptinezumab at any dose (10 to 1000 mg) across the entire development programme, 1,872 of these were exposed for ≥6 months and 991 for ≥12 months. At the dose range of 30 to 300 mg in the pivotal studies, 1,372 patients had received at least 1 dose, 1,252 patients were exposed for ≥6 months and 536 patients for ≥12 months. At the highest recommended dose of 300 mg, 823 patients were exposed at least once, 531 for ≥6 months and 177 for ≥12 months. In study 013, 86 patients were exposed to 300 mg over 8 treatments (= 24 months).
The most common adverse events were upper respiratory tract infections, but with no higher frequency compared to placebo. Most serious adverse events (SAEs) in the pivotal studies also occurred with similar frequency (1.3% under active, 1.5% under placebo) compared to the placebo groups and were based on other medical conditions. There were 2 patients with SAEs of suicidal attempts and 2 with suicidal ideation under active drug (total 3 SAEs of suicidality, since 1 SAE of ideation and 1 attempt occurred in the same patient). These patients had a history of psychiatric conditions such as depression, anxiety or posttraumatic stress disorder (PTSD). According to the treatment emergent adverse events (TEAEs) documentation, 11 cases (0.6%) of suicidal ideation occurred under active treatment, 3 (0.4%) under placebo. Most events were of mild severity, 1 of moderate severity (including self-cutting). There were 14 reported TEAEs of hypersensitivity in the active treatment arms, 13 of which led to study drug discontinuation, and no such events in the placebo arms. One case was considered as possible anaphylaxis, but without relevant respiratory or cardiovascular effects. Many of the discontinuations were protocol-driven, and none of the hypersensitivity reactions were serious or severe. Constipation (which is probably an effect related to CGRP antagonists) occurred three times more frequently in the active groups, but no severe events were documented. Higher frequency in the active groups was also noted for anxiety and nervousness and panic attacks. No relevant differences between active and placebo groups were recorded for vital signs, including for ECG or laboratory findings. A trend for increase in BMI was noted for the active groups. Anti-drug antibodies (ADAs) had an overall incidence of 16% in the studies, with 7% neutralising antibodies. No influence of ADAs on efficacy or safety was noted, but ADAs were associated with lower Ctrough levels. Overall, the safety profile can be regarded as acceptable and similar to the already approved CGRP antagonists.

For further details, please see the “Undesirable effects” and the “Warnings and precautions” sections of the information for healthcare professionals.

## 6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Eptinezumab is a monoclonal antibody administered via intravenous infusion for the prevention of migraine attacks. It binds to the CGRP ligand, and prevents the interaction with the CGRP receptor, which is considered to play a role in migraine attacks. It is administered intravenously every 3 months. The applicant has studied the efficacy and safety of eptinezumab in two randomised, double-blind, placebo-controlled clinical trials in migraine patients.
A study in patients with episodic migraine (study 006) demonstrated efficacy of eptinezumab in the reduction in monthly migraine days, based on the primary efficacy endpoint of change from baseline in frequency of migraine days over weeks 1-12. The primary endpoint was statistically significant for the 100 mg and 300 mg doses, and reduced migraine days by means of 3.9 and 4.3 days, respectively, compared to 3.2 days in the placebo arm, with a mean treatment effect of -0.7 and -1.1 migraine days, which is considered as a rather moderate effect. Responder analyses (e.g. 50% reduction in migraine days vs. baseline) showed clinically relevant effects.
The study in patients with chronic migraine (study 011) demonstrated the efficacy of eptinezumab in the reduction in monthly migraine days, based on the primary efficacy endpoint of change from



Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

baseline in the frequency of migraine days over weeks 1-12. The primary endpoint was statistically significant for the 100 mg and 300 mg doses, and monthly migraine days were reduced by a mean of 7.7 and 8.2 days, respectively, compared to 5.6 days in the placebo group, for a mean treatment difference of -2.0 and -2.6 migraine days, which is a clearly relevant effect. Key secondary endpoints of 50% and 75% migraine responders and reduction in acute migraine medication days were supportive of the primary endpoint.
Eptinezumab is generally well tolerated and had an acceptable safety profile with a low frequency of adverse events, with predominantly hypersensitivity reactions noted in the migraine population.
Data from the pivotal trials for patients aged 65 years and older is limited to n=23 patients.
Patients with clinically significant cardiovascular diseases were excluded from participation in the pivotal trials so that no safety data are available for this patient population.
Overall, the benefit-risk ratio for intravenous eptinezumab 100 mg and 300 mg given every 3 months is regarded as positive for the prophylaxis of episodic and chronic migraine.
The safety profile of eptinezumab is regarded as acceptable and is in line with the safety profile of the other already approved CGRP antagonists.

## 6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.



Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

# 7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.



Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

# 8 Appendix

## 8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Vyepti, concentrate for solution for infusion was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

**Note:**
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.



Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

## VYEPTI®

### Composition

*Active substances*

*Eptinezumab is a recombinant humanised monoclonal antibody produced in Pichia pastoris yeast cells.*

*Excipients*

L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, 40.5 mg sorbitol (E420) and Water for Injection.

### Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion (i.v.)
One vial of 1 mL contains 100 mg eptinezumab (100 mg/mL)

### Indications/Uses

Prophylactic treatment of migraine in adults, if indicated.

### Dosage/Administration

The indication for the therapy must be made by a doctor with experience in the field of migraine treatment, who also accompanies further treatment.
As for other infusion treatments, Vyepti treatment should be supervised by healthcare professionals.
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 “Properties/Effects”).
If there is insufficient response to therapy, or after 12 months at the latest, a re-evaluation should be carried out to continue the therapy. There are limited data on the safety and efficacy after 12 months.

*Missed dose:*
In case of a missed dose, administer the next dose as soon as possible and continue the quarterly dosing schedule.

*Mode of administration*

Eptinezumab is for intravenous infusion only after dilution.
For instructions on dilution of the medicinal product prior to administration, see "Other information".

*Special dosage instructions*

*Elderly patients (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. No dose adjustment is required in the elderly patients as the pharmacokinetics of Vyepti were not affected by age.

*Renal impairment/hepatic impairment*

No dose adjustment is required in patients with mild to moderate renal impairment or hepatic impairment (see "Kinetics in specific patients groups"). Patients with severe renal /hepatic impairment were not examined.

*Paediatric population (under 18 years)*

The safety and efficacy of eptinezumab in children and adolescents below the age of 18 years has not yet been established. Currently no data are available. Vyepti should therefore not be used in this age group.

*Traceability*

To ensure the traceability of biotechnologically produced medicinal products, it is recommended that the trade name and batch number are documented for each treatment.

**Contraindications**

Hypersensitivity to the active substance eptinezumab or any of the excipients listed under Composition.

**Warnings and precautions**

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 Undesirable effects). If a serious hypersensitivity reaction occurs,

administration of VYEPTI should be discontinued immediately and appropriate therapy initiated. No data are available on re-exposure to eptinezumab after (mild) hypersensitivity reactions, which could be more severe upon re-uptake of treatment.

Cardiovascular risk

Patients with a history of cardiovascular disease were excluded from clinical studies (see “Properties/Effects, Clinical efficacy”). No safety data are available in these patients.

*Paediatric population*

The safety and efficacy of Vyepti in children and adolescents has not yet been established. Vyepti should therefore not be used in this age group.

*Sorbitol*

This medicinal product contains 40.5 mg of sorbitol in each mL. The additive effects of simultaneously applied drugs containing sorbitol (or fructose) and the intake of sorbitol (or fructose) via food must be taken into account. Patients with hereditary fructose intolerance (HFI) must not receive this medicine unless it is absolutely necessary.
Before using this medicinal product, a detailed medical history of symptoms of HFI must be taken in each patient.

**Interactions**

*Pharmacokinetic 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 300mg 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.

**Pregnancy, lactation**

*Pregnancy*

There is a very limited amount of 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 “Preclinical data”). 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 absolutely necessary

*Lactation*

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. Therefore, a decision should be made about whether to discontinue breastfeeding or discontinue Vyepti, considering the potential benefit of Vyepti to the mother and the potential benefit of breastfeeding.

*Fertility*

The effect of eptinezumab on fertility in men has not been evaluated. Animal studies with eptinezumab showed no impact with respect to fertility (see “Preclinical data”).

**Effects on ability to drive and use machines**

No corresponding studies have been conducted. However, based on the available data, it is expected that Vyepti has no or negligible influence on the ability to drive and use machines.

**Undesirable effects**

A total of over 2000 patients (more than 1,600 patient years) have been treated with eptinezumab 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).

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 (see “Warnings and precautions”).

The adverse events presented below are 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).

*Infections and Infestations*
Common: Nasopharyngitis

*Immune system disorders*

Common: Hypersensitivity reactions like angioedema, urticaria, facial flushing, rash and pruritus
Rare: Anaphylactic reaction

*General disorders and administration site conditions*
Uncommon: Infusion site extravasation

*Gastrointestinal disordersGastrointestinal disorders*
Uncommon: Constipation

Description of specific undesirable effects and additional information

*Hypersensitivity reactions*
Serious hypersensitivity reactions, including anaphylactic reactions, have been reported and may develop within minutes of the infusion (see section Warnings and Precautions). 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 and 3% of patients on 100 mg in PROMISE 1 and PROMISE 2.

*Immunogenicity*
As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to eptinezumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In placebo-controlled pivotal clinical studies, PROMISE 1 (up to 56 weeks) and PROMISE 2 (up to 32 weeks), the incidence of anti-eptinezumab antibodies across both studies was 18% (105/579) and 20% (115/574) in patients receiving 100 mg and 300 mg every 12 weeks dosing, respectively.
In both studies, the incidence of anti-eptinezumab antibodies peaked at Week 24. The incidence of neutralizing antibodies across both studies was 8.3% (48/579) and 6.1% (35/574) for the 100 mg and 300 mg treatment groups, respectively.

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

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

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

**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.

**Properties/Effects**

*ATC code*

N02CD05

*Mechanism of action*

Eptinezumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds with low picomolar affinity (4 and 3 Pm KD, respectively) to α- and β- forms of human CGRP (calcitonin gene-related peptide)-ligand by inhibiting its biological activity.
Elevated blood concentrations of CGRP have been associated with migraine attacks. In addition, CGRP infusions can trigger a migraine-like attack in some patients with a history of migraines.
The exact mechanism of action for eptinezumab in the prevention of migraine attacks is not known. It is assumed that the prevention of migraine is mediated, among others, by a modification of nociception in the trigeminal system.

*Pharmacodynamics*

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

*Clinical efficacy*

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 ≤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.

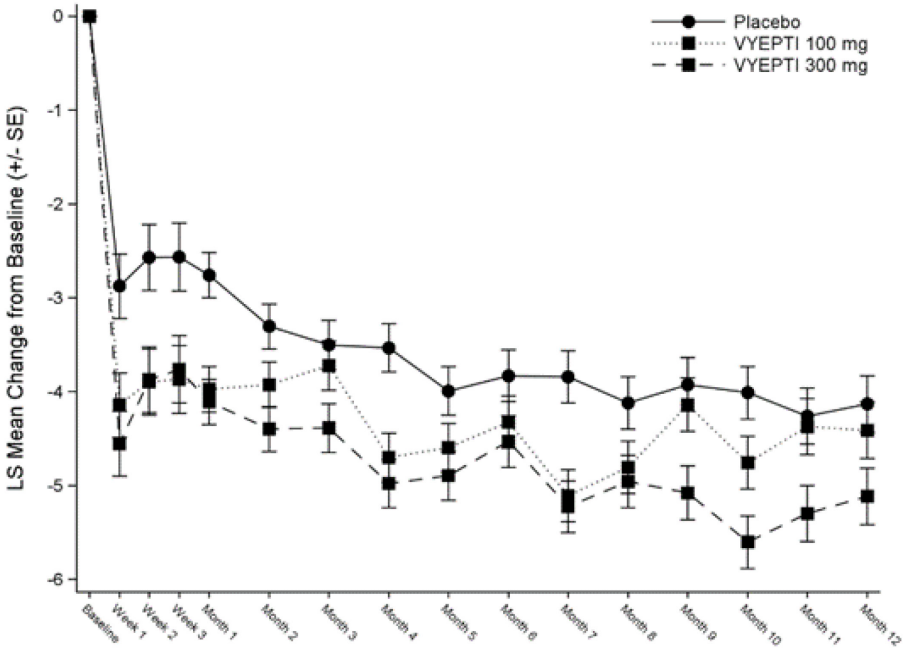
PROMISE 1: Episodic Migraine

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. A total of 665 patients were randomized and received 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 to use 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 subjects with a migraine on the day after the first dosing (Day 1).

The 4-week results over Weeks 1-48, following 4 quarterly infusions of Vyepti treatment are presented as change 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 to Week 48.

**Figure 1 Mean Changes from Baseline in Mean Monthly Migraine Days over Time 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.

Vyepti treatment demonstrated statistically significant and clinically meaningful improvements for primary and key secondary efficacy endpoints, as summarized in Table 1.

**Table 1: 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 1-12 | | | |
| 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 | |

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

PROMISE 2: Chronic Migraine

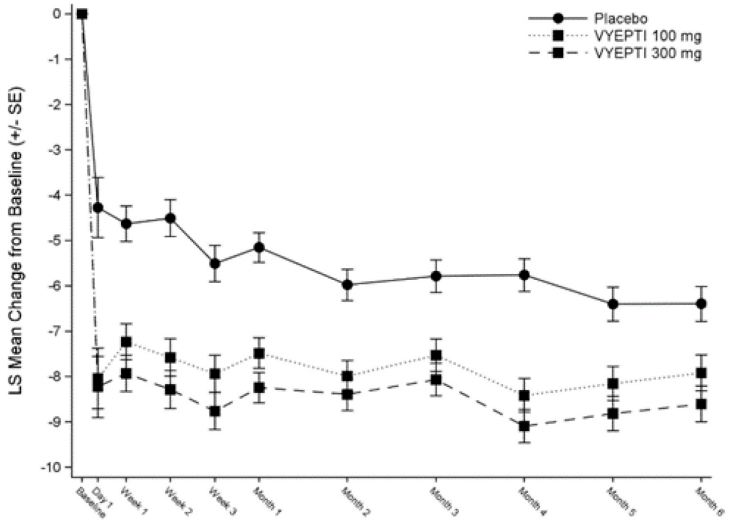
PROMISE 2 was a parallel group, double-blind, placebo-controlled global study to evaluate the efficacy and safety of VYEPTI for the preventive treatment of chronic migraine in adults. A total of 1,072 patients were randomized and received placebo (N=366), 100 mg eptinezumab (N=356), or 300 mg eptinezumab (N=350) every 12 weeks for 24 weeks (2 infusions). During the trial, 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 subjects 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.

The monthly results over Weeks 1-24, following two quarterly infusions of VYEPTI treatment are presented as change 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 2: Mean Changes from Baseline in Mean 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.

Eptinezumab treatment demonstrated statistically significant and clinically meaningful improvements for key efficacy endpoints as summarized in Table 2.

**Table 2: 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 1-12 | | | |
| 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[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] The endpoint for the 100 mg dose was not a pre-specified key secondary endpoint.

Subjects 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 subjects with chronic migraine, similar reductions in MMD (Mean for Weeks 1-12) were observed in subjects with and without MOH at baseline. The mean change from baseline in MMD (Weeks 1-12) for the subjects with MOH was for 300 mg: -8.6, 100 mg: -8.4, placebo: -5.4 and for subjects 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 subjects with MOH was (300 mg: -3.2 [95% CI: -4.66; -1.78], 100 mg: -3.0 [-4.56; -1.52]) and for subjects 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 (see “Undesirable effects”) 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 female, 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 subjects 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 migraine-related life impact, improvements in measures of health-related quality of life, and overall improvement in global impressions of change (PGIC) scale in migraine over 2 years of treatment in adults with chronic migraine. The safety profile

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

**Pharmacokinetics**

*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). Steady-state is attained after the first-dose during a once every 12 weeks dosing schedule. The mean accumulation ratios based on Cmax and AUC0-tau are 1.08 and 1.15, respectively. The exposure increases with doses of 100 to 300 mg proportionally

*Distribution*

Population pharmacokinetic analysis estimated the central volume of distribution (Vc) for eptinezumab to approximately 3.7 liters.

*Metabolism*

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

*Elimination*

Population pharmacokinetic analysis estimated the apparent clearance of eptinezumab to 0.15 L/day, and the terminal elimination half-life to approximately 27 days.

*Kinetics in specific patient groups*

*Influence of Age, Gender, Race or Body Weight*
A population pharmacokinetic analysis including 2123 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 outcome. No dose adjustment is needed based on body weight. Also, no dose adjustments are necessary based on age, gender or ethnic origin.

*Hepatic or Renal 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 mild or moderate renal or hepatic impairment that would require dose adjustment. Patients with severe renal/hepatic impairment were not examined.

## Preclinical 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.

*Mutagenicity*

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

*Carcinogenicity*

No carcinogenicity studies have been performed with eptinezumab. No carcinogenicity risk has been identified by extensive evaluation of the literature related to inhibition of CGRP and no eptinezumab-related proliferative findings were observed in long term studies in monkeys..

*Reproductive toxicity*

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 and after lactation, including behavioral or reproductive performance (rats).
For all studies, the NOAEL was the highest dose tested (150 mg/kg) which is 30-fold higher than the highest recommended human dose, based on body weight.

*Studies in juvenile animals*

Weekly intravenous treatment of juvenile rats with eptinezumab (50 or 150 mg/kg) from day 28 to day 91 postpartum did not show any adverse effects on the development.

## Other information

*Incompatibilities*

In the absence of compatibility studies, no other medications should be administered through the infusion set or mixed with Vyepti (except for the 0.9% Sodium Chloride solution in polyvinyl chloride bags or polyethylene bags mentioned in “Instructions for handling”).

*Shelf life*

Do not use this medicine after the expiry date ("EXP") stated on the container
The diluted preparation for infusion is not preserved and is intended for single use only.
Chemical and physical in-use stability of the diluted solution has been demonstrated for 8 hours when stored at room temperature (15-25°C) or refrigerated (2-8°C).

For microbiological reasons, the dilution should be used immediately, unless the dilution has been prepared in controlled and validated aseptic conditions.
If the solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.
Following dilution, the ready-to-use VYEPTI solution for infusion (VYEPTI and 0.9% Sodium Chloride for Injection) must be infused within 8 hours

*Special precautions for storage*

Keep out of the reach of children.
Store in a refrigerator (2 - 8°C) in the original container and protected from light. Do not freeze.

*Instructions for handling*

The product requires dilution with 0.9% Sodium Chloride solution in polyvinyl chloride bags or polyethylene bags 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. 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 (polyvinyl chloride bags or polyethylene bags) of 0.9% Sodium Chloride for Injection should be used to prepare the Vyepti solution for infusion as described below.

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

If stored at 2 to 8°C, allow the Vyepti solution for infusion to warm to room temperature prior to infusion.

100 mg dose:
To prepare the Vyepti solution for infusion, withdraw 1.0 mL of Vyepti from the vial using a sterile needle and syringe. Inject the 1.0 mL (100 mg) content into a 100 mL bag (polyvinyl chloride bags or polyethylene bags) of 0.9% Sodium Chloride for Injection

300 mg dose:
To prepare the Vyepti solution for infusion, withdraw 1.0 mL of Vyepti from 3 vials using a sterile needle and syringe. Inject the resulting 3.0 mL (300 mg) content into a 100 mL bag (polyvinyl chloride bags or polyethylene bags) of 0.9% Sodium Chloride for Injection.

Infuse Vyepti 100 mg or 300 mg as prescribed, following dilution of the vial content in a 100 mL bag (polyvinyl chloride bags or polyethylene bags) 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 bolus injection.

**Authorisation number**

67995 (Swissmedic)

**Packs**

Concentrate for solution for infusion (100 mg/mL 1 mL vial (B)

**Marketing authorisation holder**

Lundbeck (Schweiz) AG, Opfikon

**Date of revision of the text**

October 2021

11102021FI