NATIONAL PHARMACEUTICAL REGULATORY AGENCY
MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY

FOR FACILITATED REGISTRATION PATHWAY (FRP)

Reference drug regulatory agency: European Medicine Agency (EMA)

PRODUCT NAME:
Vyepti 100 mg/ mL concentrate for solution for infusion (MAL24086006AZ)

ACTIVE INGREDIENT:
Eptinezumab 100 mg/mL

PRODUCT REGISTRATION HOLDER:
Lundbeck Malaysia Sdn. Bhd.

PRODUCT MANUFACTURER:
Vetter Pharma-Fertigung GmbH Co.KG, Ravensburg Baden-Wuerttemberg, Germany

BATCH RELEASER:
H.Lundbeck A/S, Valby, Denmark

APPROVAL DATE:
1 August 2024 (DCA 399)

1.0 BACKGROUND INFORMATION

1.1 Approved Indication

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

1.2 Approved Posology

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 *Pharmacodynamic properties*).

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 *Pharmacokinetic properties).*

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 *Special precautions for disposal and other handling.*

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.

1.3 Method of administration

Intravenous use only after dilution

1.4 Pharmacological Aspects

Mechanism of action

Eptinezumab is a recombinant humanized immunoglobulin G1 (IgG1) antibody that binds to α- and β-forms of human calcitonin gene-related peptide (CGRP) ligand with low picomolar affinity (4 and 3 pM Kd, respectively). Eptinezumab prevents the activation of the CGRP receptors and hence the downstream cascade of physiological events linked to initiation of migraine attacks.

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

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

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 (Vc) for eptinezumab was approximately 3.7 litres.

Biotransformation

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

Elimination

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

Special Populations

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

Renal or hepatic impairment

No dedicated hepatic or renal impairment studies were conducted to assess the effects of hepatic and renal impairment upon the pharmacokinetics of eptinezumab. Population pharmacokinetic analysis of integrated data from the VYEPTI clinical studies did not reveal any differences in patients with renal or hepatic impairment that would require dose adjustment. No data for patients with severe renal impairment are available.

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Substance

- Eptinezumab is a recombinant humanized anti-calcitonin gene related peptide (CGRP) monoclonal IgG1 antibody that is produced in a yeast based expression system, Pichia pastoris. Eptinezumab has a molecular weight of 143 283 Daltons, composed of two heavy chains of 441 amino acids and two light chains of 219 amino acids. The light and heavy chain variable regions are comprised of both human and humanized rabbit sequences.
- The manufacturing process consist of the upstream process (inoculum production, seed fermentation and production fermentation) followed by the downstream process (centrifugation and flocculation, filtration, protein A chromatography, ceramic hydroxyapatite chromatography, hydrogen interaction chromatography, UF/DF, filling and packaging of the bulk drug substance). The manufacturing process has been described accordingly and considered to be satisfactory.
- Process validation has been provided on three consecutive batches. Eptinezumab bulk drug substance which met all the predefined ranges for each process step, demonstrating that the upstream and downstream manufacturing process is capable of reproducibly producing Eptinezumab bulk drug substance. The release specification for eptinezumab include tests for general characteristics and physicochemical properties, identity, quantity, purity and impurities, potency, microbial content and endotoxin. The specifications for the drug substance are the same as those approved with the EMA.
- Stability data from three batches have been provided to support the shelf life of 72 months when stored at ≤ -60°C. All results are within the acceptance criteria. Stability data on batches at accelerated condition (5°C) for 6 months are also provided. All results are within specifications.
- GMP Compliance of the drug substance manufacturer was verified by Austrian Medicines and Medical Devices Agency (BASG).

2.1.2 Finished Product

- The manufacturing process for the drug product starts with the compounding of the polysorbate 80 stock solution, followed by the thawing of the Eptinezumab bulk drug substance, formulating the finished product solution, pre-filtration for bioburden reduction, sterile filtration, aseptic filling and stoppering of vials, sealing, visual inspection and labeling and storage of the vials. The IPCs, hold times and processing times, critical process parameter have been adequately described.

- Process validation results demonstrated that the manufacturing process is capable of consistently producing drug product in accordance to the pre-defined specifications. The release and shelf life specification have been described.
- Long term stability studies results demonstrated that the finished product is stable at 48 months when stored at 2°C - 8°C to support the shelf life of 3 years. Stability data from six PPQ batches according to the ICH guidance has been provided. Accelerated storage conditions (25 ± 2°C/60 ± 5% RH) was conducted for 6 months. Results are all within the predefined acceptance criteria.
- Forced degradation were also conducted at 2°C - 8°C. Photostability studies demonstrated that the finished product is susceptible to photo degradation and must be protected from long term light exposure. In-use stability data has demonstrated that the finished product diluted with 0.9% NaCL is stable to be stored at room temperature (below 25ºC) or refrigerated at 2°C - 8°C for 8 hours.
- The drug product is a clear to slightly opalescent, colorless to brownish-yellow concentrate for solution for infusion. Each vial contains 1 mL of drug product and the concentration is 100 mg/mL. The pH of the formulation is 5.8. The product is packaged in a Type I glass vial closed with a chlorobutyl rubber stopper and secured with a seal with a flip off plastic cap.
- The product has passed the evaluation on analytical protocol and method validation in accordance with the ICH Q2 (R1) guidelines.
- GMP Compliance of the drug product manufacturer was verified by Regierungspraesidium Tuebingen, Leistelle Arzneimitteleuberwachung Baden-Wuerttemberg. The final batch releaser for this product is H. Lundbeck A/S, Valby, Denmark. The GMP compliance for this site was verified by Danish Medicine Agency.

2.2 Non-clinical studies

- The pivotal toxicology non-clinical safety studies were conducted according to the OECD GLP principles.
- Binding affinity of eptinezumab to human, rat and rabbit CGRP forms was found to be comparable except for a lower affinity to rabbit α- CGRP. Functional activity of eptinezumab was demonstrated in a cell-based assay of CGRP-induced accumulation of intracellular cAMP. In this assay, eptinezumab inhibited accumulation of intracellular cAMP induced by human, rat and rabbit α- and β-CGRP with comparable potency in the low nM range. The amino acid sequence was identical for α-and β-CGRP in human and cynomolgus monkeys and therefore not tested in monkeys.

- In vivo pharmacodynamics studies were based on clinical data as they are no animal models for migraine. These in vivo models were conducted in rat, rabbit and cynomolgus monkeys to assess the ability of eptinezumab to inhibit CGRP mediated neurogenic vasodilation in the skin. Results demonstrated Eptinezumab was well tolerated and inhibited increases in dermal blood perfusion at doses up to 100mg/kg in rats and 0.1 to 100mg/kg in monkeys and increased dermal blood perfusion secondary to intradermal β-CGRP challenge in the rabbit.
- Safety pharmacology was conducted as part acute and repeat dose toxicology studies in rat and cynomolgus monkeys which demonstrated eptinezumab was well tolerated and induced no functional effects upon the central nervous or renal systems in rats or monkeys or upon cardiovascular or respiratory systems in monkeys.
- Pharmacokinetic studies were conducted in rats and cynomolgus monkeys as part of single dose toxicity and repeat dose toxicity after IV administration. In both rats and cynomolgus monkeys the PK characteristics of eptinezumab after single IV administration was studied. Exposure to eptinezumab was generally dose-proportional. Plasma concentration profiles were consistent with IV administration.
- After repeated IV administration, in rats, the accumulation ratio in AUC was approximately 1.50 to 2.22 after once weekly dosing for 4 weeks. In cynomolgus the accumulation ratio in AUC was approximately 2.03 to 2.61-fold with once weekly dosing for 4 weeks and approximately 2.60 with dosing every 2 weeks.
- In the reproductive and development toxicity studies, there were no eptinezumab-related effects on mating, fertility or sperm assessment at doses up to 150 mg/kg. In females, there were no eptinezumab-related effects on estrous cycles, mating index or conception rate. In mated females, the numbers of corpora lutea, implantation sites, live embryos and resorptions were unaffected by the administration of eptinezumab. However there appeared to be a greater percentage of pre-implantation losses in the eptinezumab-treated females (10.82% at 75 mg/kg and 7.46% at 150 mg/kg) compared to the control group (2.39%). But this was justified to be not related to eptinezumab.
- In the local tolerance study conducted as part of the repeat dose toxicity study in rats and cynomolgus monkeys, there were no injection site gross findings, erythema or oedema, or toxicologically significant eptinezumab-related microscopic lesions observed in the injection sites of any dose route in either species.
- Based on extensive evaluation of the literature related to inhibition of CGRP, angiogenesis, and tumour growth, as well as the absence of eptinezumab-related proliferative findings from long-term studies in monkeys no further nonclinical studies on carcinogenic risk are considered necessary.

- In conclusion, the completed non-clinical studies provided for Vyepti are considered adequate and sufficient to support a positive benefit risk profile.

2.3 Clinical

- Migraine is a paroxysmal neurological disease characterized by recurrent episodes of moderate to severe headache. In the phase 3 pivotal studies, episodic migraine has been described by headaches occurring on less than 15 days per month for at least 12 months, which, on at least 4 days per month, has the features of migraine with or without aura. Chronic migraine is described by headaches occurring on 15 or more days per month for at least 12 months, which, on at least 8 days per month, has the features of migraine.

- The PROMISE phase 3 pivotal studies provide the efficacy and safety of eptinezumab in the prevention of migraine in adults with EM (PROMISE-1) and CM (PROMISE-2).

Summary of pivotal clinical studies conducted are as follows:

<table>
<tr><th>Study Type & Design (N)</th><th>Objective (s) of the Study</th><th>Results of Primary Endpoint</th></tr>
<tr><td>PROMISE-1 (ALD403-CLIN-006)

Phase 3, multicenter, parallel-group, double-blind, randomized, placebo-controlled study.

Ashina, M, et al. Eptinezumab in episodic migraine: a randomized,</td><td>To evaluate the efficacy and safety of eptinezumab, a humanized anti-calcitonin gene-related peptide monoclonal antibody, in the preventive treatment of episodic migraine.</td><td><u>Primary endpoint</u>
<table><tr><td colspan="5">Monthly migraine days (MMD) – Weeks 1-12</td></tr><tr><td></td><td>30mg</td><td>100mg</td><td>300mg</td><td>Placebo</td></tr><tr><td>Baseline</td><td>8.7</td><td>8.7</td><td>8.6</td><td>8.4</td></tr><tr><td>Mean Change</td><td>-4.0</td><td>-3.9</td><td>-4.3</td><td>-3.2</td></tr><tr><td>Difference from placebo</td><td>-0.82</td><td>-0.69</td><td>-1.11</td><td></td></tr><tr><td>95% CI</td><td>(-1.39,-0.25)</td><td>(-1.25,-0.12)</td><td>(-1.68, -0.54)</td><td></td></tr><tr><td>p-value vs placebo</td><td>0.0046*</td><td>0.0182</td><td>0.0001</td><td></td></tr></table>* Not statistically significant per the testing hierarchy

Conclusion: A single dose of eptinezumab 100 mg or 300 mg administered</td></tr>
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<tr>
<td>double-blind, placebo-controlled study (PROMISE-). Cephalalgia 40. 3 (2020): 241-254.

Ratio: 1:1:1:1

N= 223 to 30mg
N= 221 to 100mg
N= 222 to 300mg
N= 222 to placebo</td>
<td></td>
<td>by IV infusion provided a statistically significant reduction in mean monthly migraine days versus placebo and the difference was observed from the first day after administration and maintained through 12 weeks.

Within the statistical testing hierarchy, eptinezumab 30 mg did not achieve statistical significance for any of the prespecified primary and key secondary endpoints. Clinical results with eptinezumab 30 mg were less consistent over the same 12-week treatment period. Exposure following the administration of 30 mg eptinezumab was insufficient to meet the EC90 estimates. This 30mg dose however was not studied further in the phase 3 clinical trial in chronic migraine patients.</td>
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<tr>
<td>PROMISE-2 (ALD403-CLIN-011)

Phase 3, multicenter, parallel-group, double-blind, randomized, placebo-controlled study.

Lipton, Richard B., et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. Neurology 94.13 (2020): e1365-</td>
<td>To evaluate the efficacy and safety of eptinezumab, a humanized anti–calcitonin gene-related peptide monoclonal antibody, in the preventive treatment of chronic migraine (CM).</td>
<td><u>Primary endpoint</u>

<table>
<tr><td colspan="4">Monthly migraine days (MMD) – Weeks 1-12</td></tr>
<tr><td></td><td>100mg</td><td>300mg</td><td>Placebo</td></tr>
<tr><td>Baseline</td><td>16.1</td><td>16.1</td><td>16.2</td></tr>
<tr><td>Mean Change</td><td>-7.7</td><td>-8.2</td><td>-5.6</td></tr>
<tr><td>Difference from placebo</td><td>-2.0</td><td>-2.6</td><td rowspan="3"></td></tr>
<tr><td>95% CI</td><td>(-2.9, -1.2)</td><td>(-3.4,-1.7)</td></tr>
<tr><td>p-value vs placebo</td><td><0.0001</td><td><0.0001</td></tr>
</table>

Conclusion: In patients with CM, both the eptinezumab 100 mg and 300 mg dose groups provided a statistically significant reduction in mean monthly migraine days versus placebo and the difference was observed from the first day after administration and maintained through 12 weeks.</td>
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e1377. Ratio: 1:1:1 N= 356 to 100mg N= 350 to 300mg N= 366 to placebo		

- Both treatment regimens, 100 mg and 300 mg, demonstrated to be efficacious in the treatment of EM and CM.
- While 300 mg seems to have a more pronounced treatment effect across all treatment groups, the number of hypersensitivity reactions is higher in the 300 mg group compared to the 100 mg group. Weighing the benefits and risks of treatment, the proposed posology with a recommended starting dose of 100 mg, with the option to increase to the 300 mg dose for patients who do not have a sufficient response after at least 12 weeks of treatment.

2.4 Safety

- The most common adverse reactions in the clinical studies were nasopharyngitis and hypersensitivity.
- The most frequently occurring infusion-site related adverse event of special interest (AESI) was infusion site extravasation, which occurred in < 1% eptinezumab and placebo subjects.
- There was no impact of anti-drug antibody (ADA) or neutralizing ADA on efficacy or safety of eptinezumab.
- In a PREVAIL long-term safety study, the safety profile was consistent with the safety profiles observed in the randomized, placebo-controlled studies (PROMISE-1 and PROMISE-2), and a sustained effect on patient-relevant outcomes was observed for up to 96 weeks.
- In summary, the totality of clinical safety data establishes that eptinezumab is considered safe and well tolerated when administered every 12 weeks by IV infusion for the prevention of migraine in adults.

3.0 CONCLUSION

Drug Control Authority (DCA) on the 399th meeting on 1st August 2024 has decided to approve the registration of this product with the following indication:

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