CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Eptinezumab (Vyepti)

Indication: Indicated for the prevention of migraine in adults who have had at least 4 migraine days per month.

Sponsor: Lundbeck Canada Inc.

Recommendation: Reimburse with Conditions

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CADTH

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that eptinezumab be reimbursed for the prevention of migraine in adults who have had at least 4 migraine days per month only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Three multicentre, double-blind, randomized controlled trials (RCTs) (DELIVER, PROMISE-1 and PROMISE-2) demonstrated that treatment with eptinezumab 100 mg and 300 mg given intravenously every 12 weeks for 24 to 48 weeks resulted in added clinical benefit compared to placebo for patients with episodic migraine (EM) or chronic migraine (CM). Of the 3 included trials, DELIVER was the only trial that exclusively enrolled patients with a history of at least 2 prior prophylactic treatments. DELIVER demonstrated that treatment with eptinezumab was associated with statistically significant and clinically meaningful reduction in migraine frequency relative to placebo based on the change from baseline in the number of monthly migraine days (MMD) from weeks 1 to 12 (100 mg: by 2.7 days [95% CI, –3.4 to –2.0], $p<0.0001$; 300 mg: by 3.2 days [95% CI, –3.9 to –2.5], $p<0.0001$). The results of the DELIVER trial also demonstrated a benefit for treatment with eptinezumab 100 mg and eptinezumab 300 mg relative to placebo based on the key secondary outcomes, such as 50% and 75% reduction in MMD from baseline to weeks 1 to 12, change from baseline in MMD from baseline to weeks 13 to 24, and change from baseline in the Headache Impact Test (HIT-6). Patients identified a need for a preventive treatment that reduces the frequency of headaches and migraines, reduces symptoms of migraine, is well-tolerated, and improves quality of life, some of which may be met with eptinezumab.

At the sponsor submitted price for eptinezumab 100 mg and publicly listed price for comparators, eptinezumab was more costly than other anti-calcitonin gene-related peptide (anti-CGRP) therapies used as a preventative treatment for migraines in adults. There was insufficient evidence to support a clinical benefit with eptinezumab versus relevant anti-CGRP comparators, as such total treatment cost of eptinezumab should not exceed the total treatment cost of the lowest cost anti-CGRP comparator.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. The patient has a confirmed diagnosis of EM or CM according to the International Headache Society criteria, defined as: 1.1. EM: migraine headaches on at least 4 days per month and less than 15 headache days per month for more than 3 months. 1.2. CM: headaches for at least 15 days per month for more than 3 months of which at least eight days per month are with migraine.	DELIVER included a mixed population of patients with EM or CM. PROMISE-1 and PROMISE-2 enrolled patients with EM and CM, respectively. All three RCTs provided evidence that eptinezumab is superior to placebo in reducing the mean MMDs in patients with EM and CM.	—
2. The patient has experienced an inadequate response, intolerance, or contraindication to at least two oral prophylactic migraine medications.	The DELIVER trial included adults with EM or CM who had documented inadequate response to at least 2 classes of prior preventive treatment.	Inadequate response to oral prophylactic therapies is defined as less than a 30% reduction in frequency of headache days to an adequate dose and duration of at least two prophylactic medications, which must be of a different class. At least 1 of the 2 prophylactic medications previously used must have been discontinued because of lack of therapeutic effectiveness. Oral prophylactic therapies to be considered include: • beta blockers • tricyclic antidepressants • verapamil or flunarizine • sodium valproate (or divalproex sodium) • topiramate • gabapentin. A list of previously tried oral prophylactic medications, including doses and duration, and reasons for discontinuance, should be provided by the requesting physician. There is no evidence to support the combination of eptinezumab with onabotulinumtoxinA; therefore, these drugs should not be used together.
3. The physician must provide the number of headache and migraine days per month at the time of initial request for reimbursement	See Initiation Condition 1 and Renewal Condition 5.	—

Reimbursement condition	Reason	Implementation guidance
4. The maximum duration of initial authorization is six months.	Authorization of funding for 6 months provides flexibility to accommodate the practical challenges of assessing clinical response after 3 months of treatment. The 6-month-long maximum duration of authorization is also consistent with the duration recommended for other migraine prophylactic medications reviewed previously by CDEC.	—
Renewal		
5. The physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a reduction of at least 50% in the average number of migraine days per month at the time of first renewal compared with baseline. At subsequent renewals the physician must provide proof that the initial 50% reduction in the average number of migraine days per month has been maintained.	50% reduction in the number of monthly MMDs was a predefined secondary end point in each of the included RCTs.	Some jurisdictions may want to include a reduction of at least 30% in the number of headache days per month and an improvement of at least five points in the HIT-6 score, compared with baseline, as an alternative criterion for renewal of reimbursement. Jurisdictions that choose to include this criterion should also request that the physician provide the score obtained on the HIT-6 at the time of initial request for reimbursement.
6. The maximum duration of subsequent authorizations following the initial authorization is 6 months.	See initiation criterion 4.	—
Prescribing		
7. The patient should be under the care of a physician who has appropriate experience in the management of patients with migraine headaches	Accurate diagnosis of migraine is important to ensure that eptinezumab is prescribed to the appropriate patients. In addition, several migraine prophylaxis treatment options must be considered when selecting the most appropriate therapy for patients who are refractory to one or more first-line options.	—
Pricing		
8. Eptinezumab should be negotiated so that the total cost does not exceed the cost of treatment with the least costly anti-CGRP reimbursed for the preventative treatment of EM or CM in adults.	[redacted] As such, there is insufficient evidence to justify a cost premium for eptinezumab over the least expensive anti-CGRP reimbursed for the preventative treatment of EM or CM in adults.	—

CDEC = Canadian Drug Expert Committee; CGRP = calcitonin gene-related peptide; CM = chronic migraine; EM = episodic migraine; HIT-6 = Headache Impact Test.

Discussion Points

- Migraine is a common and debilitating neurologic disease that may lead to poor quality of life, social isolation, and an inability to participate in daily activities. CDEC discussed patient and clinician input that current prophylactic medications do not benefit everyone with migraine and have adverse effects that may make them difficult to tolerate, leading to poor adherence and non- achievement of desired outcomes.
- CDEC discussed the unmet therapeutic need in treatment-refractory EM and CM and noted eptineuzmab may provide an additional treatment option for patients.
- Comparative evidence was limited to indirect treatment comparisons of eptinezumab compared against other medications used to prevent migraines. The results of the NMA submitted by the sponsor [redacted] were inconclusive due to methodological limitations with the analysis. Also, the indirect comparison did not assess safety. As such, it is uncertain that eptinezumab would address needs that are not currently addressed through other prophylactic treatments for migraine.
- Long-term efficacy and safety cannot be established based on the results of the 24-week DELIVER and PROMISE-2 trials, and 48-week PROMISE-1 trial, in which patients received 2 infusions or 4 infusions of eptinezumab, respectively. The PREVAIL trial assessed the longer term (up to 104 weeks) safety and patient reported outcomes; however, methodological issues with the PREVAIL trial, including the absence of a comparator arm, creates uncertainty regarding long-term safety of eptinezumab.
- Improvement in quality of life and a reduction in adverse events were identified as outcomes of importance to patients. Although HRQOL instruments were included in the clinical trials, none of the statistical testing procedures were controlled for multiplicity, which limits any conclusions that can be drawn regarding this important outcome. Regarding adverse events, no comparative safety evidence (direct or indirect) for eptinezumab and other CGRP inhibitors or onabotulinum toxin A was identified.
- CDEC noted the lack of evidence regarding combination use of eptinezumab with onabotulinum toxin A and other medications used for prevention of migraines is an important gap in evidence. CDEC also discussed that in clinical practice, patients on migraine prophylaxis treatments frequently discontinue or switch treatments due to lack of efficacy or tolerability, which is not supported by the evidence for eptinezumab.
- CDEC noted the difference in the method of administration between eptinezumab (IV injection) and other CGRP inhibitors (subcutaneous injection). The use of IV infusion may be associated with increases in health care resource utilization (e.g., infusion time, nursing time, etc.). Given the insufficient evidence to support a difference in comparative efficacy between treatments, it is important that the drug price for eptinezumab is lower than the drug price of the least costly CGRP inhibitor to account for these differences in total treatment cost.
- CDEC noted that the sponsor's pharmacoeconomic submission priced a 300 mg dose based on three vials of the 100 mg dose, as a 300 mg dose was not yet available. [redacted] Should a 300 mg dose not be made available, or should a different price be introduced for a 300 mg dose, the price should be negotiated such that the total treatment cost with the 300 mg dose does not exceed the total treatment cost of the least costly CGRP inhibitor.

Background

Migraine is a complex neurological disorder whose precise cause is not completely understood. Patients with migraine report migraine attacks that are characterized by severe headache (throbbing, diffuse pain), accompanied by other symptoms such as nausea/vomiting, dizziness, sensory hypersensitivity, and tingling or numbness in the extremities and/or face. Migraines can occur with or without aura, and the aura is characterized by a wide range of primarily neurological symptoms that can affect vision, speech, sensations, muscle strength and cognitive function. All of these symptoms associated with migraine can impair quality of life. Based on a study published in 2011, in Canada, at least 2.6 million adult females and almost 1 million adult males have migraine, although this may be an underestimation, as not everyone who has migraine seeks medical help and therefore do not have an official diagnosis. Approximately three quarters of patients experiencing migraine report impaired function, and one-third require bed rest during a migraine attack.

There are two approaches to treating migraine: management of acute attacks and prophylaxis, the latter of which is typically only considered for those with more frequent migraines (≥4 migraine days per month). Topiramate is an oral anticonvulsant that is indicated in adults for the prophylaxis of migraine headache. Onabotulinum toxin A has a Health Canada indication for chronic migraine prophylaxis and was previously reviewed by CADTH. The calcitonin gene-related peptide receptor (CGRP) inhibitors (erenumab, fremanezumab, galcanezumab, and eptinezumab) have been approved by Health Canada for the prevention of migraine. Many other therapies used for migraine prophylaxis are used off-label, as they lack an official indication for this purpose from Health Canada. Broadly speaking, the main categories are antidepressants, anti-convulsants and cardiovascular drugs. While they are well-established drugs, they all have various tolerability issues for patients, and this is important given that they are to be used on a chronic basis in migraine prophylaxis.

Eptinezumab has been approved by Health Canada for the prevention of migraine in adults who have at least 4 migraine days per month. Eptinezumab is a CGRP binding antibody. It is available as 100 mg/mL solution for intravenous infusion and the dosage recommended in the product monograph 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.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a systematic review of 3 double-blind randomized controlled trials in adult patients with either episodic migraine or chronic migraine, frequent episodic migraine, and chronic migraine
- patients perspectives gathered by 2 patient groups, Migraine Canada and Migraine Quebec
- input from public drug plans that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with migraine
- no clinician group input was received
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from one clinical expert consulted by CADTH for the purpose of this review.

Patient Input

- Patient input was provided as a joint submission by two groups, Migraine Canada and Migraine Quebec, for the review of eptinezumab, and data was collected via 2 online surveys, as well as direct input from patients who have experience with eptinezumab who reside in the US.

- Patients report migraine as impacting their quality of life and sleep, mental health, social relationships and day to day functioning at work and school. Patients believe that improving quality of life, decreasing the frequency and the intensity of headaches as well as symptoms other than pain are key outcomes of interest.
- According to the surveys conducted in 2021 and 2022, 30% and 24% of respondents reported having found a preventative treatment that provided greater than 50% improvement in frequency and intensity of migraine with no significant side effects. According to the 2021 survey, 66% of respondents reported discontinuing their preventative medication due to side effects. Additionally, 57% of respondents in the 2021 survey indicated they had not filled their prescription in the past 6 months due to lack of coverage.

Clinician input

Input from clinical experts consulted by CADTH

- The clinical expert consulted by CADTH on this review identified the following as unmet needs: patients who have a delayed response with migraine prevention treatment, patients whose migraines are refractory to current treatment options, lack of therapies that reverse the course of the disease, and bioavailability (lack of an intravenous formulation).
- With respect to place in therapy, the clinical expert believed that eptinezumab would complement onabotulinum toxin A, and that ideally eptinezumab would be first line along with other CGRP mAbs, however they also noted that in real-world use eptinezumab is likely to be used as a later treatment due to cost and insurance coverage requirements.
- The clinical expert noted that the patients most likely to benefit from eptinezumab are those with episodic migraine (EM) or chronic migraine (CM). The patients most in need of an intervention such as eptinezumab are those having difficulty self-administering subcutaneous injections, chronic daily headache, and those with medication overuse headache (MOH).
- According to the clinical expert, a clinically meaningful response could include a reduction in monthly headache days (MHD) and monthly migraine days (MMD) and a 50% responder (50% reduction in MMD). The clinical expert also indicated that patient reported outcomes should also be taken into account, as well as a reduction in use of acute medications for migraine.
- Indications for discontinuing treatment, according to the clinical expert, would include lack of response after a 6 month trial, intolerable side effects, allergy/anaphylaxis, patient preference, or switching to another CGRP monoclonal antibody (mAb) due to inconvenience with intravenous administration.

Clinician group input

No clinician group input was received for the review of eptinezumab.

Drug Program Input

Table 2. Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
In the pivotal studies for eptinezumab, the comparator was placebo, while other therapies for the prevention of migraine may have been appropriate comparators.	*Comment from the drug programs to inform CDEC deliberations.*
Considerations for initiation of therapy	
The sponsor reimbursement request is for patients have experienced an inadequate response, intolerance, or contraindication to at least two oral prophylactic migraine medications (as per the CDEC initiation criteria fremanezumab and galcanezumab). The sponsor also indicated that there is growing evidence that a patient not appropriately responding to one anti-CGRP antibody may respond better to another one. Should prior treatment with another preventative therapy, including other anti-CGRP antibodies, be considered when determining eligibility for reimbursement of eptinezumab?	The clinical expert noted that some patients may respond to alternative CGRP despite failure to a previous CGRP and it is not possible to identify who those patients are in advance. The clinical expert believed that ideally, eptinezumab would be used first-line along with other CGRP mAbs, however due to limitations such as cost and coverage reimbursement will likely only be considered after a trial or 2 oral prophylaxis treatments. CDEC indicated that if reimbursement is to be recommended, it should be consistent with how jurisdictions currently fund CGRP

Implementation issues	Response
	mAbs. Additionally, it was noted that the DELIVER trial excluded patients with prior anti-CGRP antibodies use.
The CDEC initiation criteria for fremanezumab and galcanezumab is as follows: 1. The patient has a confirmed diagnosis of episodic or chronic migraine according to the International Headache Society criteria, defined as: 1.1. Episodic migraine: migraine headaches on at least 4 days per month and less than 15 headache days per month for more than 3 months. 1.2. Chronic migraine: headaches for at least 15 days per month for more than 3 months of which at least eight days per month are with migraine. 2. The patient has experienced an inadequate response, intolerance, or contraindication to at least two oral prophylactic migraine medications. 3. The physician must provide the number of headache and migraine days per month at the time of initial request for reimbursement. 4. The maximum duration of initial authorization is six months. Should the initiation criteria for eptinezumab be aligned with that of fremanezumab and galcanezumab?	The clinical expert agreed with all the initiation criteria described for fremanezumab and galcanezumab, with the exception of the maximum duration of initial authorization. The clinical expert noted that 6 months is not enough time to adequately evaluate response, given that eptinezumab is administered every 3 months. The clinical expert believed that up to 1 year for initial authorization would be more clinically appropriate. CDEC indicated that if reimbursement is to be recommended, it should be consistent with how jurisdictions currently fund CGRP mAbs.
Considerations for continuation or renewal of therapy	
The CDEC renewal criteria for fremanezumab and galcanezumab is as follows: 1. The physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a reduction of at least 50% in the average number of migraine days per month at the time of first renewal compared with baseline. At subsequent renewals the physician must provide proof that the initial 50% reduction in the average number of migraine days per month has been maintained. 2. The maximum duration of subsequent authorizations following the initial authorization is 6 months. Should the renewal criteria for eptinezumab be aligned with that of fremanezumab and galcanezumab?	The clinical expert believed that if the 50% reduction criterion was not fulfilled, the specialist should be given the opportunity to provide a rationale for continued use given that not every patient will achieve a 50% reduction. The clinical expert suggested that using a 30% reduction and a reduction in HIT-6 (5 points) for eligibility for renewal. CDEC indicated that if reimbursement is to be recommended, it should be consistent with how jurisdictions currently fund CGRP mAbs.
Considerations for prescribing of therapy	
The recommended dose of eptinezumab is 100 mg administered by IV infusion every 12 weeks. Some patients may benefit from a dosage of 300 mg administered by IV infusion every 12 weeks. The need for dose escalation	The clinical expert stated that there is a lack of data on switching between doses and therefore uncertainty exists on this issue. The clinical expert believed this would depend on the cost of the drug. If eptinezumab 300mg is 3 times the cost of eptinezumab 100mg, if a patient fails at least 2 doses of 100mg then at least 2 doses of 300mg will be tried next. If eptinezumab 300mg is the

Implementation issues	Response
should be assessed within 12 weeks after initiation of the treatment. Are there any cases in which a patient should receive the 300mg dose immediately without first trialing the 100mg dose? i.e., would immediate reimbursement of the 300mg dose be a valid option in certain cases?	same/similar cost to eptinezumab 100mg, the clinical expert suggested offering 300mg to patients who are refractory at the first visit, depending on patient characteristics. CDEC was in agreement with the response from the clinical expert consulted by CADTH. Further, CDEC noted that the [redacted]
Eptinezumab is administered via intravenous infusion by a healthcare professional and requires availability of infusion clinics and trained healthcare professionals.	*Comment from the drug programs to inform CDEC deliberations.*
CADTH recommendations for galcanezumab and fremanezumab state that since there is no evidence for combination usage of the respective therapies with onabotulinum toxin A, therefore they should not be used together. Is there any evidence to support the combination usage of eptinezumab with onabotulinum toxin A, compared with the previous agents and onabotulinum toxin A?	The clinical expert noted that there is no data for eptinezumab combined with onabotulinum toxin A, but noted that there is data for onabotulinum toxin A combined with other monoclonal antibodies. Based on this, the clinical expert suggested that eptinezumab could be used with onabotulinum toxin A. CDEC was in agreement with the response from the clinical expert consulted by CADTH.
System and economic issues	
Currently, a 300 mg SKU is not available and is still under development. In economic components of the submission, the 300 mg dose is costed linearly with the 100 mg dose since the only way to obtain a 300 mg dose is by purchasing three 100 mg/mL vials. Compared with eptinezumab 300 mg, eptinezumab 100 mg was found to be less costly and less effective. Following the review of eptinezumab by CADTH, Lundbeck Canada Inc. plans to address the 300 mg dose cost with the pCPA and to provide participating drug plans [redacted]	*Comment from the drug programs to inform CDEC deliberations.*

CDEC = Canadian Drug Expert Committee; CGRP = calcitonin gene-related peptide; CM = chronic migraine; EM = episodic migraine; HIT-6 = Headache Impact Test; mAb = monoclonal antibody; pCPA = pan-Canadian Pharmaceutical Alliance.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

There were 3 pivotal sponsor-funded multicentre double-blind (DB) randomized controlled trials (RCTs) included in this review, each comparing 2 different doses of eptinezumab, 100mg and 300mg every 12 weeks, to placebo. In DELIVER, 892 patients with either EM or CM, in PROMISE-1, 674 patients with frequent EM and in PROMISE-2 1050 patients with CM were randomized at a ratio of 1:1:1 to each of the eptinezumab 100mg, eptinezumab 300mg or placebo groups. In each study, patients received 2 doses of eptinezumab or placebo, one at baseline and one at week 12. The primary outcome in each of the 3 studies was the change from baseline to weeks 1 to 12 in MMD. Key secondary outcomes, all controlled for multiplicity, included the number of patients achieving at least a 75% or at least a 50% reduction in MMD, the number of patients with migraine one day after dosing, migraine prevalence on days 1 to 28 post-dose, change from baseline in headache impact test (HIT)-6 scores and acute medication usage.

In DELIVER, mean age of patients was approximately 44 years, while in the PROMISE studies the mean age of patients was approximately 40 years. In all studies, the majority of patients were female, approximately 90% in DELIVER, 84% in PROMISE-1 and 88% in PROMISE-2, and White (96% in DELIVER, 84% in PROMISE-1 and 91% in PROMISE-2). In DELIVER, 60% of patients

had EM, and [redacted] had 14 or fewer MHDs and there were 62% with 2 prior migraine prophylaxis failures, 31% with 3 prior failures, and 7% with 4 prior failures, and 12% had a diagnosis of MOH. In PROMISE-1, 36% had greater than 9 MMD, and in PROMISE-2 45% had 17 MMD or greater.

Efficacy Results

In DELIVER, for weeks 1 to 12, MMD was estimated to be reduced among patients on eptinezumab compared to those on placebo by 2.7 days for the 100mg dose ([95% CI: -3.4; -2.0], p<0.0001|) and by 3.2 days for the 300mg dose ([95% CI: -3.9; -2.5], p<0.0001). For weeks 13 to 24 MMD was estimated to be reduced among patients on eptinezumab compared to those on placebo by 3.0 days for the 100mg dose ([95% CI: -3.8; -2.2], p<0.0001) and by 3.7 days for the 300mg dose ([95% CI: -4.5; -3.0], p<0.0001). These comparisons were statistically significant based on the pre-specified sequence of testing. Sensitivity analyses of the primary outcome were consistent with that of the primary analysis. In PROMISE-1, for weeks 1 to 12, MMD was estimated to be reduced among patients on eptinezumab by 0.7 days for the 100mg dose ([95% CI: -1.3; -0.1], p=0.0182) and by 1.1 days for the 300mg dose ([95% CI: -1.7; -0.5], p<0.0001). These comparisons were statistically significant based on the pre-specified sequence of testing. Results of the sensitivity analyses were consistent with that of the primary analysis. For weeks 13 to 24, MMD was estimated to be reduced among patients on eptinezumab by [redacted] on the 100mg dose ([redacted]) and by [redacted] on the 300mg dose ([redacted]). These comparisons fell outside of the multiple testing procedure (MTP) therefore no p-values are reported here. In PROMISE-2, for weeks 1 to 12, MMD was estimated to be reduced among patients on eptinezumab by 2.0 days for the 100mg dose ([95% CI: -2.9; -1.2], p=<0.0001) and by 2.6 days for the 300mg dose ([95% CI: -3.4; -1.7], p<0.0001). These comparisons were statistically significant based on the pre-specified sequence of testing. For weeks 13 to 24 MMD was estimated to be reduced among patients on eptinezumab by 2.0 days for the 100mg dose (95% CI: -2.9; -1.0) and by 2.7 days for the 300mg dose (95% CI: -3.6; -1.7). These comparisons fell outside of the MTP therefore no p-values are reported here. Results of the sensitivity analysis were consistent with that of the primary analysis. No formal pre-specified subgroup analyses of the primary outcome were performed for PROMISE-1 and PROMISE-2. In DELIVER, pre-specified subgroup analyses of the primary outcome were conducted with no control for multiplicity. [redacted]

50% reduction in MMD

In DELIVER, the proportion of patients achieving a 50% or greater reduction in MMD at weeks 1 to 12 was 42% in the eptinezumab 100mg group, 50% in the eptinezumab 300mg group, and 13% with placebo, with an OR in the eptinezumab 100mg group of 4.91 (95% CI: 3.29; 7.47; p<0.0001) and in the eptinezumab 300mg group of 6.58 (95% CI: 4.41; 10.01; p<0.0001). These comparisons were statistically significant based on the pre-specified sequence of testing. Proportion of patients achieving a 50% or greater reduction in MMD at weeks 1 to 12 was also reported in PROMISE-1, with a mean difference in proportions between eptinezumab 100mg and placebo of 12.4% ([95% CI: 3.2, 21.5]) and between eptinezumab 300mg and placebo of 18.9% ([95% CI: 9.8, 28.0], p=0.0001). The comparison between eptinezumab 300mg and placebo was statistically significant based on the pre-specified sequence of testing, however the p-value for the comparison between eptinezumab 100mg and placebo will not be reported here due to early failure of the hierarchy. Proportion of patients achieving a 50% or greater reduction in MMD at weeks 1 to 12 was also reported in PROMISE 2 with a difference in proportions between eptinezumab 100mg and placebo of 18.2% ([95% CI: 11.1, 25.4], p<0.0001) and between eptinezumab 300mg and placebo of 22.1% ([95% CI: 14.9, 29.2], p<0.0001). These comparisons were statistically significant based on the pre-specified sequence of testing.

75% reduction in MMD

In DELIVER, proportion of patients achieving a 75% or greater reduction in MMD at weeks 1 to 12 was 16% in the eptinezumab 100mg group, 19% in the eptinezumab 300mg group, and 2% with placebo, for an OR in the eptinezumab 100mg group of 9.19 (95% CI: 4.16; 24.35; p<0.0001) and in the eptinezumab 300mg group of 11.43 (95% CI: 5.22; 30.15; p<0.0001). These comparisons were statistically significant based on the pre-specified sequence of testing. Proportion of patients achieving a 75% or greater reduction in MMD weeks 1 to 4 was also reported in PROMISE-1, with a difference in proportions between eptinezumab 100mg and placebo of 10.5% (95% CI: 2.4, 18.6, p=0.0112) and between eptinezumab 300mg and placebo of 11.3% (95% CI: 3.2, 19.3, p=0.0066), both in favour of eptinezumab. These comparisons were statistically significant based on the pre-specified sequence of testing. From weeks 1 to 12 in PROMISE-1, the difference in proportions between eptinezumab 100mg and placebo was 6.0% ([95% CI: -1.4, 13.3], p=0.1126) and between eptinezumab 300mg and placebo was 13.5% ([95% CI: 5.8, 21.2], p=0.0007). The

comparison between eptinezumab 300mg and placebo was statistically significant based on the pre-specified sequence of testing, however the comparison between eptinezumab 100mg and placebo was not statistically significant, and this is where the hierarchy failed in PROMISE-1. Proportion of patients achieving a 75% or greater reduction in MMD at weeks 1 to 4, was also reported in PROMISE-2, with a difference in proportions between eptinezumab 100mg and placebo of 15.3% (95% CI: 9.3, 21.4) and between eptinezumab 300mg and placebo of 21.3% (95% CI: 15.0, 27.6; p<0.0001). These comparisons were statistically significant based on the pre-specified sequence of testing. From weeks 1 to 12, the difference between eptinezumab 100mg and placebo was 11.7% (95% CI: 5.8, 17.5, p<0.0001) and between eptinezumab 300mg and placebo was 18.1% (95% CI: 12.0, 24.3, p<0.0001). These comparisons were statistically significant based on the pre-specified sequence of testing.

100% reduction in MMD

In DELIVER, proportion of patients achieving a 100% or greater reduction in MMD (100% responders) was also reported, weeks 1 to 12, eptinezumab 100mg versus eptinezumab 300mg versus placebo of 5.9% versus 7.7% versus 1.1%. 100% responders were reported for weeks 1 to 4, eptinezumab 100mg, eptinezumab 300mg and placebo, in PROMISE-1 (9% versus 15% versus 6%, respectively) and in PROMISE-2 (8% versus 13% versus 3%). 100% responders were also reported for weeks 9 to 12, eptinezumab 100mg, eptinezumab 300mg and placebo, as 13%, 16% and 10%, respectively in PROMISE-1 and 11%, 17% and 6% in PROMISE-2.

Patients with migraine the first day after dosing

The proportion of patients who had a migraine the first day after dosing was a secondary outcome of DELIVER. From a baseline of [redacted] of patients with migraine, on the first day after dosing 27.2% had a migraine in the eptinezumab 100mg group, while from a baseline of [redacted], 24.4% had a migraine the day after dosing in the eptinezumab 300mg group, and in placebo, from a baseline of [redacted], 43.7% had a migraine the first day after dosing. Proportion of patients with a migraine the first day after dosing was a key secondary outcome of PROMISE-1 and PROMISE-2. In PROMISE-1, from a baseline of 31.0% with migraine, 14.8% of patients had a migraine the day after dosing in the eptinezumab 100mg group, and from a baseline of 30.8% with migraine, 13.9% had a migraine the day after dosing in the eptinezumab 300mg group, and in placebo, from a baseline of 29.8% with migraine, 22.5% had a migraine the day after dosing. The p-values reported by the sponsor were tested after failure of the statistical hierarchy and will not be reported here. In PROMISE-2, from a baseline of 57.5% of patients with migraine, 28.6% had a migraine the day after dosing in the eptinezumab 100mg group, from a baseline of 57.4% with migraine, 27.8% had migraine the day after dosing in the eptinezumab 300mg group, and with placebo, from a baseline of 58.0% with migraine, 42.3% had a migraine the day after dosing. When compared to placebo, the differences between eptinezumab 100mg and placebo (p<0.0001) and eptinezumab 300mg and placebo (p<0.0001) were statistically significant based on the pre-specified sequence of testing.

Headache frequency

In DELIVER, the MHD mean ±SE change from baseline to weeks 1 to 12 for eptinezumab 100mg was -4.6 ±0.37 (from a baseline of 14.5 ±5.6), for eptinezumab 300mg was -5.1 ±0.37 (from a baseline mean ±SD of 14.4 ±5.5) and for placebo was -2.1 ±0.38 (from a baseline mean ±SD of 14.5 ±5.8). Change from baseline in MHD was not part of the MTP and therefore p-values were not reported. In PROMISE-1, the difference in the mean change from baseline to weeks 1 to 12 in MHD versus placebo for eptinezumab 100mg was [redacted] from a baseline mean ±SD of 10.0 ±3.0, and eptinezumab 300mg was [redacted] from a baseline mean ±SD of 10.1 ±3.1. Change from baseline in MHD was not part of the MTP and therefore p-values were not reported. In PROMISE-2, the difference in the mean change from baseline to weeks 1 to 12 in MHD versus placebo for eptinezumab 100mg was -1.7 (95% CI: -2.6; -0.9) from a baseline mean ±SD of 20.4 ±3.1 and eptinezumab 300mg was -2.3 (95% CI: -3.2; -1.4) from a baseline mean ±SD of 20.4 ±3.2. Change from baseline in MHD was not part of the MTP and therefore p-values were not reported.

Acute medication use

In DELIVER, for weeks 1-12, monthly days using migraine medications was estimated to be reduced among patients on eptinezumab compared to those on placebo by 2.5 days (from a mean ±SD baseline of 11.2 ±5.5 days) for the 100mg dose ([95% CI: -3.2, -1.9]) and by 3.0 days (from a mean ±SD baseline of 11.0 ±5.3 days) for the 300mg dose ([95% CI: -3.6, -2.4]). In DELIVER, for weeks 13-24 monthly days using migraine medications was estimated to be reduced among patients on eptinezumab compared to those on placebo by 2.9 days for the 100mg dose (95% CI: -3.6, -2.2) and by 3.5 days for the 300mg dose (95% CI: -4.2, -2.8).

The above comparisons were not part of the MTP therefore p-values are not reported here. In PROMISE-1, for weeks 1-12, monthly days using migraine medications was estimated to be reduced among patients on eptinezumab compared to those on placebo by 0.5 days (from a mean ±SD baseline of 1.5 ±2.6 days) for the 100mg dose (95% CI: -0.7, -0.3) and by 0.4 days (from a mean ±SD baseline of 1.6 ±2.7 days) for the 300mg dose (95% CI: -0.6, -0.2). No p-values are reported here because this outcome was not part of the MTP. In PROMISE-2, for weeks 1-12, monthly days using migraine medications was estimated to be reduced among patients on eptinezumab compared to those on placebo by 1.2 days (from a mean ±SD baseline of 6.6 ±6.9 days) for the 100mg dose (95% CI: -1.7, -0.7) and by 1.4 days (from a mean ±SD baseline of 6.7 ±6.5 days) for the 300mg dose ([95% CI: -1.9, -0.9], p<0.0001). No p-value is reported here for the 100mg dose in PROMISE-2 because testing was not part of the MTP.

Other PRO

PGIC scores were reported in DELIVER, and the difference at week 24 versus placebo was [redacted] in the eptinezumab 100mg group and was [redacted] in the eptinezumab 300mg group. PGIC was not part of the MTP therefore p-values are not reported here. Improvement in PGIC scores was reported as a binary outcome in PROMISE-2, with the percentage of patients who were 'very much improved', eptinezumab 100mg versus eptinezumab 300mg versus placebo, of [redacted], and 'much improved', [redacted], respectively. This outcome was not assessed in PROMISE-1.

HRQOL

In DELIVER, the change from baseline to week 24 in EQ-5D-5L VAS score was estimated to be improved among patients on eptinezumab compared to those on placebo by 4.7 points (from a baseline mean ±SD of 75.9 ±[redacted]) for the 100mg dose (95% CI: 1.8, 7.7) and by 8.0 points (from a baseline mean ±SD of 74.5 ±[redacted]) for the 300mg dose (95% CI: 5.1, 10.8). In PROMISE-1, the EQ-5D-5L VAS mean (SD) change from baseline to week 24 for eptinezumab 100mg was [redacted] and eptinezumab 300mg was [redacted] and for placebo was [redacted]. In PROMISE-2, the EQ-5D-5L VAS mean (SD) change from baseline to week 32 for eptinezumab 100mg was [redacted] and eptinezumab 300mg was [redacted] and for placebo was [redacted]. Positive changes indicate improvement on this scale.

In DELIVER, for the MSQ, the change from baseline to week 24 in the role function restrictive domain was estimated to be improved among patients on eptinezumab compared to those on placebo by 15.1 points (from a baseline mean ±SD of 35.7 ±[redacted]) for the 100mg dose (95% CI: 11.7, 18.5) and by 15.0 points (from a baseline mean ±SD of 35.7 ±[redacted]) with the 300mg dose (95% CI: 11.6, 18.4). For the MSQ role function preventive domain, the mean change from baseline to week 24 was estimated to be improved among patients on eptinezumab compared to those on placebo by 12.6 points (from a mean ±SD baseline of 50.2 ±[redacted]) for the 100mg dose (95% CI: 9.4, 15.8) and by 13.2 points (from a mean ±SD baseline of 51.0 ±[redacted]) for the 300mg dose (95% CI: 10.1, 16.4). For MSQ emotional function domain, the change from baseline to week 24 was estimated to be improved among patients on eptinezumab compared to those on placebo by 14.1 points (from a mean ±SD baseline of 50.3 ±[redacted]) for the 100mg dose (95% CI: 10.5, 17.7) and by 14.1 points (from a mean ±SD baseline of 48.6 ±[redacted]) for the 300mg dose (95% CI: 10.6, 17.7).

Symptoms

In DELIVER, the mean (SE) change from baseline to week 12 in the HIT-6 score was estimated to be decreased (improved) among patients on eptinezumab compared to those on placebo by -3.8 points (from a mean ±SD baseline of 66.6 ±4.7) for the 100mg dose (95% CI: -5.0, -2.5; p<0.0001) and by -5.4 points (from a mean ±SD baseline of 66.5 ±4.4) for the 300mg dose (95% CI: -6.7, -4.2; p<0.0001). In PROMISE-2, the mean (SE) change from baseline to week 12 in the HIT-6 score was estimated to be decreased (improved) among patients on eptinezumab compared to those on placebo by -1.7 points (from a mean ±SD baseline of 65.0 ±4.9) for the 100mg dose (95% CI: -2.8, -0.7; p<0.0001) and by -2.9 points (from a mean ±SD baseline of 65.1 ±5.0) for the 300mg dose (95% CI: -3.9, -1.8; p<0.0001).

In DELIVER, MBS scores were also reported under symptoms, and the mean (SE) scores at week 24 were estimated to be decreased (improved) among patients on eptinezumab compared to those on placebo by [redacted] for eptinezumab 100mg and by [redacted] for eptinezumab 300mg. In PROMISE-2, MBS scores at week 32 were reported as very much improved, eptinezumab 100mg, 300mg and placebo of [redacted], and much improved as [redacted], respectively. The HIT-6 and the MBS were not assessed in PROMISE-1.

Health Care Resource Utilization

In DELIVER, for HCRU the number of patients with no visit to a family physician, eptinezumab 100mg versus eptinezumab 300mg versus placebo was [redacted], those who had no visit to a specialist was [redacted], and those with no ED visits due to migraine was [redacted] respectively. There were few hospitalizations due to migraine [redacted] of patients in each group) and similar numbers were seen for overnight hospital stays due to migraine.

Work Days Lost

In DELIVER, the mean (SD) change from baseline to week 24 in absenteeism score on the WPAI was estimated to be decreased (improved) among patients on eptinezumab compared to those on placebo by -4.5 points (from a mean ±SD baseline of 11.4 ±[redacted]) for the 100mg dose (95% CI: -7.8, -1.1) and by -4.7 points (from a mean ±SD baseline of 12.0 ±[redacted]) for the 300mg dose (95% CI: -8.0, -1.5). Outcomes related to the loss of work days were not assessed in PROMISE-1 and PROMISE-2.

Harms Results

There were no deaths in any of the studies.

In DELIVER, adverse events (AE) were reported by 43%, 41%, and 40% of patients, 63%, 58%, and 60% of patients in PROMISE-1, and 44%, 52% and 47% of patients in PROMISE-2, who were randomized to the eptinezumab 100mg, eptinezumab 300mg and placebo groups, respectively.

Serious adverse events (SAE) occurred in 2%, 2% and 1% of patients in DELIVER, 2%, 1%, and 3% of patients in PROMISE-1, and, less than 1%, 1% and less than 1% of patients in PROMISE-2, randomized to eptinezumab 100mg, eptinezumab 300mg, and placebo, respectively. There were no SAE that occurred in more than 1 patient.

In DELIVER, treatment stoppages due to an AE occurred in 0.3% of patients in the eptinezumab 100mg and placebo groups and 2% of patients in the eptinezumab 300mg group. In PROMISE-1, there were 3% of patients in the eptinezumab 100mg and placebo groups, and 2% in the eptinezumab 300mg group who stopped treatment due to an AE, and in PROMISE-2 there were less than 1% who stopped treatment due to an AE in the eptinezumab 100mg and placebo groups, and 2% of patients in the eptinezumab 300mg group.

Notable harms identified by the review team included: anaphylaxis or hypersensitivity reactions, antibody formation, cardiovascular events, suicidality, alopecia, and fatigue. The most common notable harms in DELIVER were hypersensitivity/anaphylaxis, occurring in 2% of patients in each of the eptinezumab 100mg and placebo groups, and 3% of patients in the eptinezumab 300mg group, and cardio or cerebrovascular disorders, occurring in 3% of patients in the eptinezumab 100mg and placebo groups, and 1% in the eptinezumab 300mg group. All other notable harms occurred in 1% of patients or less, and in PROMISE-1 and PROMISE-2, notable harms occurred in 1% of patients or less.

Critical Appraisal

Issues related to internal validity included a large number of withdrawals in PROMISE-1 (>20% across groups) that may have impacted results for efficacy and harms, most notably by changing the mix of baseline characteristics in the study population. According to the sponsor, 94% of patients remained in the study at the time of the 12 week assessment for the primary and a number of key secondary outcomes, however this large number of withdrawals may have impacted results after week 12, particularly those for harms, and particularly if the patients who already discontinued the study would have been more or less likely to experience harm from continued use of eptinezumab. None of the HRQOL hypothesis testing procedures were controlled for multiplicity in any of the included studies, therefore this limits any conclusions that can be drawn from these important outcomes as the lack of control for multiple statistical comparisons increases the risk of Type 1 error.

With respect to external validity, none of the included studies featured an active comparator, therefore any comparisons to other drugs for migraine prophylaxis are indirect and the limitations of these analyses are outlined in the following section. In 2 of the 3 included studies, patients only received 2 doses of eptinezumab, for a total double blind observation period of 24 weeks. This is not of sufficient duration to adequately assess the durability of response to eptinezumab as well as the long-term harms. Although a

longer term study, PREVAIL, is available, there was no control group, and this limits any conclusions that can be drawn regarding long term efficacy or harms.

Indirect Comparisons

Description of Studies

The sponsor-submitted an unpublished network meta-analysis (NMA), informed by a systematic literature review (SLR) to identify all existing RCTs for the treatment of migraine, that aimed to compare eptinezumab with key comparators (erenumab, fremanezumab, galcanezumab, and onabotulinumtoxinA) for the prevention of EM or CM in adults and have experienced an inadequate response, intolerance, or contraindication to at least two oral prophylactic migraine medications.

A feasibility assessment was conducted by the manufacturer to assess the suitability of an NMA for the comparison of the identified studies with the DELIVER trial. A total of 11 studies were included in the Bayesian NMA, evaluating the comparative impact of eptinezumab, key CGRP mAbs, and placebo on efficacy and HRQoL in EM and CM patients. Characteristics of trials reporting on anti-CGRPs and onabotulinumtoxinA in EM and CM were assessed for heterogeneity of study characteristics, and baseline characteristics. Given the differences in treatment by migraine type, separate analyses were conducted for EM and CM.

The NMA was conducted in a Bayesian framework using fixed effect models as base case analyses due to the limited number of studies per comparison. No closed loops were formed in the networks, therefore, it was not possible to assess consistency between direct and indirect evidence.

The primary analysis of the NMA consisted of comparisons between eptinezumab and anti-CGRPs for EM and CM separately. The outcomes included in the NMA were 50% migraine response rate (MRR), change from baseline in MMD at 12 weeks, change from baseline in MMD at 12 weeks with acute medication use, change from baseline in MSQ v2.1 domains (RF-R, EF, and RF-P) at 12 weeks, 75% MRR, and change from baseline in HIT-6 at 12 weeks.

Two secondary analyses were conducted: the first consisting of comparisons with onabotulinumtoxinA for the endpoints of change from baseline in MMD and 50% MRR using data from 24 weeks for onabotulinumtoxinA and 12 weeks for eptinezumab due to limited data availability. The other secondary analysis consisted of comparisons with anti-CGRPs, adjusting for the route of administration for change from baseline in MMD at week 12 given that eptinezumab is the only treatment administered by IV, and may demonstrate greater placebo effects.

Efficacy Results

[redacted]

Harms Results

Harms were not evaluated in the sponsor-submitted NMA.

Critical Appraisal

Given the common comparator of placebo in migraine RCTs, the sponsor conducted a Bayesian NMA, which was considered appropriate. The NMA was informed by an adequately conducted SLR that included planned searches of multiple databases, conference proceedings, clinical trial registries as well as regulatory and HTA agency websites, which was recently updated to mid-2021.

The CADTH team and the clinical expert consulted by CADTH believed that the methods for the inclusion of studies in the NMA by the sponsor was reasonable but additional sources of heterogeneity were noted, yet not explored in the sponsor's feasibility

analyses, including differences in dosing schedules, and time of assessment. Concurrent with the feasibility assessment, the sponsor identified the following potential treatment effect modifiers based on the results of subgroup analyses from the included trials: medication overuse headaches (for CM patients only), baseline severity (i.e., EM versus CM and baseline MMD) and number of prior treatment failures. Given the lack of comparability of EM and CM patients due to differences in migraine frequency and severity, all analyses were separately conducted based on the diagnosis of EM or CM, as well as only including patients with 2 or more prior treatment failures.

Outcomes included in the NMA were relevant to the treatment of both EM and CM in Canada. Outcomes focused on reductions from baseline in migraine frequency (50% and 75% MRR and change from baseline in MMD [with use of acute medication]) and HRQoL (MSQ v2.1 domains and HIT-6). No outcomes related to safety were evaluated, thus the comparative safety of eptinezumab and other CGRP mAbs remains unknown.

The NMA was conducted within a Bayesian framework using fixed effects for all efficacy outcomes. Generation of model statistics (i.e., deviance information criterion) for model selection were performed, though the results were not reported. Also based on the lack of available data, only arm-level data was used for comparisons. Given the absolute outcome measures considered in the analyses, this was considered appropriate, however, arm-based models do not preserve randomization, hence comparative estimates are at a greater risk of bias in relative treatment effects.

While some NMAs suggested that eptinezumab is favoured when compared with erenumab and galcanezumab for certain outcomes (50% MRR, change from baseline in MMD) it is worth noting that the results are produced using fixed effect models, and it is uncertain if the fixed effect model is the appropriate model to use in these comparisons due to lack of reporting of DICs. As a result, superiority of eptinezumab compared with erenumab and galcanezumab cannot be concluded. Moreover, in all fixed effects analyses, results were associated with wide 95% CrIs, with most estimates crossing the threshold of no effect, resulting in notable imprecision in the results. Results for random effects analyses for the two main outcomes were generally associated with even wider 95% CrIs.

Other Relevant Evidence

One open-label, phase 3 study, PREVAIL, was summarized to provide additional information on the long-term safety and efficacy of repeated quarterly administered intravenous infusions of eptinezumab in patients with chronic migraines for the preventive treatment of chronic migraines.

Description of studies

The open-label, phase 3 study, PREVAIL, was conducted to evaluate the long-term safety of up to 8 intravenous infusions of eptinezumab 300 mg administered at 12-week intervals in 128 adult patients with chronic migraines for up to 84 weeks of treatment. The secondary objective was to evaluate the efficacy of eptinezumab by assessing its impact on patient-reported outcomes. The inclusion and exclusion criteria were generally consistent with the pivotal PROMISE-2 clinical trial. Patients were eligible to enroll into PREVAIL if they were diagnosed with migraines at ≤ 50 years of age and had a history of chronic migraines for ≥ 1 year prior to screening. The duration of the study was 106 weeks which included a 2-week screening period, 48-week primary treatment period, 36-week secondary treatment period, and 20-week follow-up period. In each treatment period, patients received 4 intravenous infusions of eptinezumab every 12 weeks; only patients who received all 4 infusions in the primary treatment period were permitted to enter the secondary treatment period. Patients were evaluated at Day 0, Weeks 2, 4, 8, and 12, and every 12 weeks thereafter. For patients who failed to receive all 4 infusions of eptinezumab in the primary treatment period or did not provide consent for participation in the secondary treatment period, they were followed-up at Weeks 48 and 56.

The mean age of patients in PREVAIL was 41.5 years (SD = 11.33). The majority of patients were female (85.2%) and White (95.3%). The mean duration of migraine diagnosis at baseline was 21.2 years (SD = 11.65). The patient-reported mean number of headache days, migraine days, and migraine attacks per 28-day period in the 3 months prior to screening was 20.3 days (SD = 3.68), 14.1 days (SD = 4.25), and 10.5 days (SD = 4.29), respectively.

A total of 128 patients were enrolled in PREVAIL and all patients received at least 1 dose of eptinezumab (Safety Population). A total of 22 patients (17.2%) prematurely discontinued the study with the most common reason being withdrawal by patient in 18 patients

(14.1%). Overall, 100 patients (78.1%) completed the study (Week 104). A total of 86 patients (67.2%) received a total of 8 doses of the study drug. The concomitant use of at least one acute and one prophylactic treatment for headaches was reported in 127 patients (99.2%) and 46 patients (35.9%), respectively.

Efficacy Results

Health-related Quality of Life

For EQ-5D-5L VAS, the mean score at baseline and Week 48 were [redacted] and [redacted], respectively, demonstrating improvement (n = 114).

Headache Symptoms

For HIT-6, the mean total score at baseline and Week 101 to 104 were 65.2 (SD = 4.76) and 56.1 (SD = 9.07), respectively, demonstrating improvement (n = 96).

At baseline, the MBS reported were sensitivity to light in 31 patients (24.2%), nausea in 14 patients (10.9%), sensitivity to sound in 10 patients (7.8%), pain with activity in 10 patients (7.8%), mental cloudiness in 4 patients (3.1%), vomiting in 2 patients (1.6%), mood changes in 2 patients (1.6%), and other symptom in 55 patients (43.0%). Most patients reported 'very much improved' (35.7%) or 'much improved' (39.3%) at Week 48 relative to baseline (n = 112). 'No change' was reported by 11 patients (9.8%). No patients reported 'minimally worse', 'much worse', and 'very much worse' at Week 48 relative to baseline.

Other Patient-Reported Outcomes

For PGIC, most patients reported 'very much improved' (49.0%) or 'much improved' (34.4%) at Week 104 relative to baseline (n = 96). 'No change' was reported by 5 patients (5.2%). No patients reported 'minimally worse', 'much worse', and 'very much worse' at Week 104 relative to baseline.

Harms Results

A total of 91 patients (71.1%) reported at least 1 TEAE, with the most common event being nasopharyngitis in 18 patients (14.1%). A total of 5 (3.9%) patients reported at least 1 serious TEAE; no single event was reported in more than 1 patient (<1%). A total of 8 patients (6.3%) reported any TEAE that led to study drug withdrawal, of which 3 patients (2.3%) reported study drug withdrawal due to hypersensitivity. No other single event was reported in more than 1 patient (1%). No deaths were reported for the duration of the study. For notable TEAEs, hypersensitivity was reported in 5 patients (3.9%), hypertension was reported in 2 patients (1.6%), and anaphylactic reaction, hypotension, and deep vein thrombosis were reported in 1 patient (< 1%) each.

Critical Appraisal

In the absence of an active comparator or placebo group, our ability to interpret the safety and efficacy results from the open label study, PREVAIL, is limited. The interpretation of the safety and efficacy results may be further limited by the missing data in patient-reported outcomes at Week 104, and only 86 patients (67.2%) received a total of all 8 doses of eptinezumab. The open label study design can bias the reporting of endpoints, particularly in any subjective measures included in the efficacy and safety parameters due to the unblinding of the study drug during the treatment period; the direction and magnitude of the bias is uncertain. Of note, 28 patients (21.9%) had participated in a prior clinical trial of eptinezumab. These patients were eligible to enroll if they had not experienced any clinically significant adverse events related to the study drug during the previous study as determined by the investigator. Consequently, these patients may be more tolerant to eptinezumab, and their inclusion may result in lower adverse event rates than would be expected in a non-selected population.

The baseline characteristics in patients with chronic migraines in PREVAIL were generally consistent with the baseline characteristics in PROMISE-2 which also included patients with chronic migraines. The clinical expert consulted by CADTH for this review had estimated that at least 80% of patients presenting with migraines in clinical practice are females; 109 patients (85.2%) were female in PREVAIL. Only eptinezumab 300 mg was evaluated in PREVAIL, therefore, the generalizability of the safety and efficacy results in the open label study to eptinezumab 100 mg is limited.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis 12-week decision tree followed by Markov model
Target population	Deviation from the Health Canada indication: Adult patients who have at least four migraine days per month and have failed two or more prior preventive treatments, in two populations: • Episodic migraines (EM; <15 headache and ≥ 4 migraines days per month) • Chronic migraines (CM; ≥8 migraines per month and ≥15 headache days per month for ≥3 months)
Treatments	• Eptinezumab 100 mg • Eptinezumab 300 mg
Dose regimen	• 100 mg or 300 mg every 12 weeks
Submitted Price	• Eptinezumab, 100 mg/mL solution vial: $1,665.00 per single-use vial
Treatment Cost	• Annual cost of $7,240 to $21,720 for the 100 mg or 300 mg dose, assumes linear pricing for the 300 mg dose
Comparators	• Fremanezumab 225 mg • Fremanezumab 675 mg • Galcanezumab 120 mg
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	5.1 years (66 cycles, including the initial 12-week decision tree)
Key data source	• Clinical efficacy of eptinezumab: DELIVER, a phase 3 double-blind, placebo-controlled trial with a 48-week dose-blinded extension • Comparative clinical efficacy data was derived from a sponsor-submitted network meta-analysis (NMA) to inform the odds of achieving ≥50% reduction in monthly migraine days (MMD) over weeks 1-12
Key limitations	• The comparative clinical effectiveness of eptinezumab to other currently available preventative migraine therapies is uncertain. In the absence of direct clinical evidence, the sponsor conducted a NMA comparing eptinezumab to erenumab, fremanezumab, galcanezumab and onabotulinumtoxinA (the latter considered only among CM patients); however, there are limitations in the NMA findings due to the heterogeneity in the included studies and lack of reporting for model statistics. • All relevant comparators in the CM base case were not considered. OnabotulinumtoxinA was not considered a relevant comparator despite a positive recommendation from CDEC in the CM patient population. While the sponsor considered onabotulinumtoxinA in a scenario analysis, comparative efficacy to eptinezumab is uncertain due to lack of head-to-head and limitations in the sponsor submitted NMA. • The model structure does not adequately reflect the management of migraine in clinical practice. Clinically meaningful aspects of the condition such as headache severity which may impact treatment were not considered in the model. • The long-term efficacy of eptinezumab is uncertain and differences in the long-term efficacy among treatments was not adequately explored.
CADTH reanalysis results	• Due to lack of head-to-head evidence for eptinezumab versus other anti-CGRPs and limitations in the sponsor submitted NMA, the CADTH reanalysis assumed that there would be no difference in treatment effects (i.e., no difference in total QALYs) and a cost comparison between eptinezumab and its comparators was conducted to highlight the differences in drug costs. [redacted]

Component	Description
	[redacted] • The annual drug cost of eptinezumab is greater than or equal to that of all other anti-CGRP comparators (incremental difference ranging from $0 to $15,335 depending on the dose of eptinezumab and its comparator). Note that eptinezumab is associated with fewer annual administration frequencies versus comparative anti-CGRPs except for fremanezumab 675 mg administrated every 3 months. • There was insufficient comparative clinical evidence to justify a price premium for eptinezumab in either CM or EM above currently available comparators. The submitted price of eptinezumab 100 mg would need to be reduced by at least 11% to be equivalent to the lowest priced reimbursed anti-CGRP. When considering linear pricing for the 300 mg dose of eptinezumab, then the submitted price would need to be reduced by 70% to be equivalent to the lowest priced reimbursed anti-CGRP

BSC = best supportive care, CM = chronic migraine, CGRP = calcitonin gene-related peptides, EM = episodic migraine, ICER = incremental cost-effectiveness ratio, LY = life-year, MMD = monthly migraine days, NMA = network meta-analysis, QALY= quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's BIA: the market share of onabotulinumtoxinA may be underestimated, which was explored in a scenario analysis. Results of the sponsor's base case suggest that the reimbursement of eptinezumab for the prevention of migraine in adults who have had at least four migraine days per month and have experienced inadequate response, intolerance, or contraindication to at least two oral prophylactic migraine medications is associated with an incremental cost of $961,199 in Year 1, $4,169,910 in Year 2, and $7,061,793 in Year 3. Therefore, the cumulative incremental budget impact over three years is expected to be $12,192,901. CADTH's scenario analyses suggest the impact of reimbursing eptinezumab is highly sensitive to the eptinezumab drug cost. In a scenario analysis assuming flat pricing for both 100 mg and 300 mg doses of eptinezumab that was no greater than the lowest reimbursed cost anti-CGRP comparator, the estimated incremental three-year budget impact was -$237,734. The budget impact of reimbursing eptinezumab for the full Health Canada population remains unknown.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: October 27, 2022

Regrets:

1 expert committee member did not attend.

Conflicts of interest:

None