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Eptinezumab

Updated: July 9, 2021.

OVERVIEW

Introduction

Eptinezumab is a humanized monoclonal antibody to calcitonin gene like peptide (CGLP) which is used in the prevention of migraine headaches. Eptinezumab is generally well tolerated and has not been associated with serum aminotransferase elevations during therapy or with instances of clinically apparent liver injury.

Background

Eptinezumab (ep" ti nez' ue mab) is a humanized IgG1 monoclonal antibody directed against the calcitonin gene-related peptide (CGRP) which plays an important role in the pathogenesis of migraine headaches. CGRP is a potent vasodilator and pain neurotransmitter, infusions of which can induce migraine headache in susceptible persons and serum levels of which are elevated in persons with migraine headaches. Eptinezumab binds to circulating and tissue expressed CGRP and prevents its binding to its receptor on vascular and neural tissue. In preregistration randomized, placebo controlled trials, eptinezumab given every 12 weeks reduced the frequency of migraines in patients with episodic migraine (<15 days of headaches monthly) and chronic migraine (≥15 days of headache monthly) by 25% to 35% compared to placebo infusions. Eptinezumab was approved in the United States in 2019 for prevention of migraine headaches in adults with frequent or severe migraines. Eptinezumab is available in single use vials of 100 mg in 1 mL under the brand name Vyepti. The recommended dose is 100 mg infused over 30 minutes every 3 months. Common side effects of eptinezumab include local injection reactions, nasopharyngitis, dizziness, headaches and fatigue. Also reported have been uncommon and generally mild-to-moderate instances of hypersensitivity reactions including angioedema.

Hepatotoxicity

In prelicensure randomized controlled trials, only rare instances of mild-to-moderate serum aminotransferase elevations were reported in patients receiving intravenous eptinezumab and all were transient, asymptomatic and did not necessitate discontinuation of eptinezumab infusions. Furthermore, there were no reported instances clinically apparent liver injury or severe hepatic adverse events attributed to the monoclonal antibody. Since approval and more general use of eptinezumab there have been no reports of clinically significant liver injury attributed to its use.

Likelihood score: E (unlikely cause of clinically apparent acute liver injury).

Mechanism of Injury

Possible mechanisms of liver injury due to eptinezumab are not known. Monoclonal antibodies and immunoglobulins are generally taken up and metabolized intracellularly to short peptides and amino acids. There is no evidence that inhibition of CGRP signaling is harmful to the liver.

Drug Class: Monoclonal Antibodies, Migraine Headache Agents

Drugs in the Subclass, CGRP Antagonists: Erenumab, Fremanezumab, Galcanezumab

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Eptinezumab – Vyepti®

DRUG CLASS

Migraine Headache Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Eptinezumab	1644539-04-7	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 09 July 2021

Abbreviations: CGRP, calcitonin gene-related peptide.

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of eptinezumab).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/761119Orig1s000SumR.pdf

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA multidisciplinary scientific review of the eptinezumab application which mentions safety results in Section 8, page 16).

Dodick DW, Lipton RB, Silberstein S, Goadsby PJ, Biondi D, Hirman J, Cady R, et al. Eptinezumab for prevention of chronic migraine: A randomized phase 2b clinical trial. Cephalalgia. 2019;39:1075–85. PubMed PMID: 31234642.

(Among 616 adults with chronic migraine treated with eptinezumab [10, 30, 100 or 300 mg] or placebo as a single intravenous infusion, a 75% reduction in number of migraine days per month occurred in 27%, 28%, 31% and 33% on drug vs 21% on placebo, and adverse events were mostly mild upper respiratory symptoms and dizziness; there were no serious adverse events and data on ALT levels were not reported).

Ashina M, Saper J, Cady R, Schaeffler BA, Biondi DM, Hirman J, Pederson S, et al. Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1). Cephalalgia. 2020;40:241–54. PubMed PMID: 32075406.

(Among 888 patients with episodic migraine treated with eptinezumab [30, 100 or 300 mg] vs placebo intravenously every 12 weeks for 48 weeks, the reduction in number of migraine days per month averaged -4.0, -3.9, -4.2 on drug vs -3.2 on placebo, and adverse events that were more frequent with drug were upper respiratory symptoms and fatigue; no mention of ALT elevations or hepatotoxicity).

Lipton RB, Goadsby PJ, Smith J, Schaeffler BA, Biondi DM, Hirman J, Pederson S, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. Neurology. 2020;94:e1365–e1377. PubMed PMID: 32209650.

(Among 1072 patients with chronic migraine treated with eptinezumab [100 or 300 mg] vs placebo intravenously at week 0 and 12, average number of migraine days per month decreased by 7.7 and 8.2 with eptinezumab and by 5.6 days with placebo, and adverse events were uncommon and usually mild, the most frequent being nasopharyngitis [9.4% vs 6%] and fatigue [1.8% vs <1%], and there were no hepatic adverse events and no mention of ALT elevations).

Dhillon S. Eptinezumab: first approval. Drugs. 2020;80(7):733–9. PubMed PMID: 32266704.

(Review of the mechanism of action, history of development, clinical efficacy and safety of eptinezumab shortly after its approval for use in the US, mentions side effects of fatigue and dizziness, but does not mention ALT elevations or hepatotoxicity).

Eptinezumab (Vyepti) for migraine prevention. Med Lett Drugs Ther. 2020;62(1599):85–7. PubMed PMID: 32555116.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of eptinezumab in relation to other drugs for migraine prevention shortly after its approval in the US, states that it is modestly effective and that adverse events include nasopharyngitis and hypersensitivity reactions [1-2%] including angioedema; no mention of ALT elevations or hepatotoxicity).

Drugs for Migraine. Med Lett Drugs Ther. 2020;62(1608):153–60. PubMed PMID: 33434187.

(Concise summary of the relative clinical efficacy, safety and costs of drugs to treat acute migraine headache [such as analgesics, opiates, triptans and ergots] and to prevent migraines [such as anticonvulsants, beta blockers, antidepressants and CGRP antagonists]).

Silberstein S, Diamond M, Hindiyeh NA, Biondi DM, Cady R, Hirman J, Allan B, et al. Eptinezumab for the prevention of chronic migraine: efficacy and safety through 24 weeks of treatment in the phase 3 PROMISE-2 (Prevention of migraine via intravenous ALD403 safety and efficacy-2) study. J Headache Pain. 2020;21:120. PubMed PMID: 33023473.

(Among 1072 adults with chronic migraine treated with eptinezumab [100 or 300 mg] vs placebo intravenously at 0 and 12 weeks, the reduction in days with migraine per month decreased by week 24 by 8.2 and 8.8 days vs 6.2 days with placebo, and no new adverse events were reported compared to [compared to Lipton 2020], hypersensitivity reactions occurring in 3 patients [0.9%] with the second dose; no mention of ALT elevations or hepatotoxicity).

Smith TR, Janelidze M, Chakhava G, Cady R, Hirman J, Allan B, Pederson S, et al. Eptinezumab for the prevention of episodic migraine: sustained effect through 1 year of treatment in the PROMISE-1 Study. Clin Ther. 2020;42:2254–65.e3. PubMed PMID: 33250209.

(Among 888 patients with episodic migraine treated with eptinezumab [30, 100, 300 mg] vs placebo intravenously every 12 weeks for up to one year, reductions in average number of days with migraine per month were 4 to 4.8

with eptinezumab vs 3.2 to 4.6 with placebo, and adverse events rates were similar in all groups and decreased after the initial dose, and "no serious tolerability signals were observed").

Kudrow D, Cady RK, Allan B, Pederson SM, Hirman J, Mehta LR, Schaeffler BA. Long-term safety and tolerability of eptinezumab in patients with chronic migraine: a 2-year, open-label, phase 3 trial. BMC Neurol. 2021;21:126. PubMed PMID: 33740902.

(Among 128 adults with chronic migraine treated with eptinezumab [300 mg] intravenously every 12 weeks for up to 2 years, adverse events included upper respiratory tract symptoms and a low rate of hypersensitivity reactions [5 patients], one of which was moderate and responded rapidly to an infusion of antihistamine; in addition, "No clinically relevant trends in clinical laboratory.…results were identified").

Smith TR, Spierings ELH, Cady R, Hirman J, Schaeffler B, Shen V, Sperling B, et al. Safety and tolerability of eptinezumab in patients with migraine: a pooled analysis of 5 clinical trials. J Headache Pain. 2021;22:16. PubMed PMID: 33781209.

(Analysis of safety based upon pooled results from five placebo controlled trials of eptinezumab in 2867 patients with migraine found an overall treatment-emergent adverse event ate of 55% [1.7% severe] with drug vs 52% [1.4% severe] with placebo, and most events were considered unrelated, although infusion related hypersensitivity reactions occurred in 1.1% of eptinezumab vs 0% of placebo recipients).

Winner PK, McAllister P, Chakhava G, Ailani J, Ettrup A, Krog Josiassen M, Lindsten A, et al. Effects of intravenous eptinezumab vs placebo on headache pain and most bothersome symptom when initiated during a migraine attack: a randomized clinical trial. JAMA. 2021;325:2348–56. PubMed PMID: 34128999.

(Among 476 adults who were treated with an intravenous infusion within 1 to 6 hours of onset of a migraine headache, the time to being pain free was shorter with 100 mg of eptinezumab than placebo [4 vs 9 hours] and adverse event rates were similar except for hypersensitivity reactions [2.1% vs none]; no mention of hepatic adverse events or ALT elevations).