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Galcanezumab

Updated: April 15, 2019.

OVERVIEW

Introduction

Galcanezumab is a monoclonal antibody to the calcitonin gene related peptide which is used for prevention of migraine in patients with episodic or chronic migraine headaches. Galcanezumab has not been associated with serum enzyme elevations during therapy nor has it been implicated in cases of clinically apparent drug induced liver injury with jaundice.

Background

Galcanezumab (gal" ka nez' ue mab) is a recombinant, humanized monoclonal antibody to the calcitonin gene related peptide (CGRP), a neuropeptide which plays an important role in migraine headaches. CGRP is found throughout the central and peripheral nervous systems and has potent vasodilator and pain-signaling activities. Circulating levels of CGRP are elevated in patients with migraines, and the efficacy of migraine therapies (serotonin receptor agonists, ergot alkaloids) is associated with lowering of CGRP levels. Galcanezumab is a CGRP antagonist and blocks the neuropeptide from binding to its receptor and the subsequent downstream activation of the intracellular signaling pathways. Galcanezumab was approved for use in the United States in 2018 as a means of prevention of migraine headaches and was one of three CGRP antagonists approved in 2018 for this indication (the others being erenumab and fremanezumab). Galcanezumab is available in solution in single use prefilled syringes or pens of 120 mg under the brand name Emgality. The recommended initial dose is 240 mg subcutaneously followed by 120 mg once monthly. Galcanezumab is not effective as therapy of acute migraine, and it lowers the frequency but typically does not abolish all episodes of chronic migraine headaches. Side effects of galcanezumab are uncommon but can include injection site and hypersensitivity reactions. Galcanezumab has not been associated with significant numbers of severe adverse events, however it has had limited general use and the effects of long term suppression of CGRP signaling are unknown, but could theoretically increase the rate of serious cardiovascular or cerebrovascular ischemic events.

Hepatotoxicity

In large clinical trials, galcanezumab was associated with isolated, rare instances of elevations in serum aminotransferase levels during therapy (<1%) and rates of most adverse reactions, except for injection site reactions, were similar to those in patients who received placebo. There have been no published reports of clinically apparent acute liver injury attributed to galcanezumab therapy. Thus, significant liver injury from galcanezumab must be rare if it occurs at all.

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

Mechanism of Injury

Galcanezumab is a humanized monoclonal antibody and is unlikely to be inherently hepatotoxic. While most recombinant proteins are metabolized by the liver, the metabolism leads largely to small peptides and amino acids which may be reused to synthesize proteins and are unlikely to be toxic or immunogenic. Galcanezumab has minimal effect on hepatic microsomal enzyme activity and has not been linked to adverse drug-drug interactions.

Drug Class: Migraine Headache Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Galcanezumab – Emgality®

DRUG CLASS

Migraine Headache Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Galcanezumab	1578199-75-3	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 15 April 2019

Abbreviations: CGRP, calcitonin gene related protein.

Zimmerman HJ. Drugs used to treat rheumatic and musculospastic disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 517-54.

(Expert review of hepatotoxicity published in 1999, well before the availability of most monoclonal antibody therapies).

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 569-91.

(Review of hepatotoxicity of monoclonal immunosuppressive agents; "the biological immuno-suppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists"; galcanezumab is not discussed).

Available at: https://www.accessdata.fda.gov/scripts/cder/daf/

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy).

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy).

Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. Cephalalgia 2018; 38: 1442-54. PubMed PMID: 29848108.

(Among 915 patients with episodic migraine treated with galcanezumab [120 or 240 mg] or placebo injections monthly for 6 months, headache days decreased more with active drug than placebo [-4.3 and -4.2 vs -2.3 days per month] and adverse event rates were similar in all 3 groups except for injection site reactions; one patient on the highest dose of galcanezumab discontinued early because of "hepatic enzyme" elevations).

Edvinsson L. The CGRP pathway in migraine as a viable target for therapies. Headache 2018; 58 Suppl 1: 33-47. PubMed PMID: 29697153.

(Review of the calcitonin gene related peptide and its receptor including their relationship to migraine headaches and development of small molecular inhibitors and monoclonal antibody therapies based upon their inhibition).

Tepper SJ. History and review of anti-calcitonin gene-related peptide (CGRP) therapies: from translational research to treatment. Headache 2018; 58 Suppl 3: 238-75. PubMed PMID: 30242830.

(Review of the role of CGRP in pathogenesis of migraine headaches and the development of small molecules and monoclonal antibody antagonists of CGRP actions).

Lamb YN. Galcanezumab: first global approval. Drugs 2018; 78: 1769-75. PubMed PMID: 30378008.

(Review of the mechanism of action, pharmacology, clinical efficacy and safety of galcanezumab shortly after its approval for use in the US; mentions that injection site reactions were the most frequent adverse effect [18%]; no mention of ALT elevations or hepatotoxicity).

Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. Neurology 2018 Nov 16. [Epub ahead of print] PubMed PMID: 30446596.

(Among 1133 patients with chronic migraine treated with galcanezumab [120 or 240 mg] or placebo injections monthly, headache days decreased more with active drug than placebo [-4.6 and -4.8 vs -2.7 days per month] while adverse event rates were similar except for injection site reactions [3% and 5% vs 2%], and 2 subjects "had a treatment-emergent abnormal hepatic enzyme", 1 on galcanezumab and 1 on placebo).

Camporeale A, Kudrow D, Sides R, Wang S, Van Dycke A, Selzler KJ, Stauffer VL. A phase 3, long-term, open-label safety study of galcanezumab in patients with migraine. BMC Neurol 2018; 18: 188. PubMed PMID: 30413151.

(Among 270 adults with episodic or chronic migraine treated with galcanezumab [120 or 240 mg] monthly for one year, headache days decreased with both doses [-5.6 and -6.5 days per month] and liver test abnormalities arose in only 4 patients, all of which were transient resolving without discontinuation).

Fremanezumab (Ajovy) and galcanezumab (Emgality) for migraine prevention. Med Lett Drugs Ther 2018; 60 (1559): 177-80. PubMed PMID: 30681655.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of fremanezumab and galcanezumab shortly after their approval for prevention of migraine; does not mention ALT elevations or hepatotoxicity).