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Eliglustat

Updated: March 5, 2018.

OVERVIEW

Introduction

Eliglustat is an oral inhibitor of glucosylceramide synthase which is used in the therapy of type 1 Gaucher disease. Clinical experience with eliglustat is limited, but it not been linked to serum enzyme elevations during therapy or to instances of clinically apparent acute liver injury.

Background

Eliglustat (el" i gloo' stat) is a small molecule inhibitor of glucosylceramide synthase, the first and rate controlling step in the pathway of glycolipid synthesis. By inhibiting the pathway, lower levels of gylcolipid substrates are available, so that less of the substrate is available for lysosomal degradation and less glycosylceramide accumulates. Eliglustat was shown to decrease the intracellular accumulation of glycosylceramide in animal models of Gaucher disease. In several randomized controlled trials, eliglustat was shown to decrease spleen and liver volume and increase hemoglobin and platelet counts in patients with type 1 Gaucher disease. Eliglustat was also able to maintain clinical benefit in patients who had been maintained on long term enzyme replacement therapy with glucocerebrosidase infusions (the lysosomal enzyme that is deficient in type 1 Gaucher disease). Eliglustat was approved as oral therapy of type 1 Gaucher Disease in the United States in 2015. Eliglustat is metabolized by the microsomal enzyme CYP 2D6 and serum levels are markedly affected by different CYP 2D6 isoenyzmes, so that it is recommended only for patients who are extensive, intermediate or poor metabolizers of CYP 2D6 and not for ultra-rapid metabolizers or patients who have an indeterminant or unknown metabolizer status. Eliglustat is available in tablets of 84 mg and the usual dose is 84 mg twice daily, but major dose adjustments are recommended for patients taking inhibitors of CYP 3A or 2D6. Side effects can include fatigue, headache, nausea, diarrhea, back pain and muscle aches.

Hepatotoxicity

In placebo controlled trials, liver test abnormalities were no more common with eliglustat than with placebo treatment, and what abnormalities occurred were mild and resolved spontaneously usually without need for dose interruption. During these premarketing clinical trials and since its more widespread clinical availability, no instances of acute liver injury with jaundice have been reported attributable to eliglustat. However, the total clinical experience with eliglustat use has been limited.

Likelihood score: E (unlikely cause of clinically apparent liver injury, but experience with its use is limited).

Mechanism of Injury

The mechanism by which eliglustat might cause serum aminotransferase elevations or liver injury is not known. Eliglustat is extensively metabolized by the liver via the cytochrome P450 system (predominantly CYP 2D6 and 3A) and is susceptible to drug-drug interactions with agents that induce or inhibit these enzymes.

Outcome and Management

The serum aminotransferase elevations that occur on eliglustat therapy are usually self-limited and do not require dose modification or discontinuation of therapy. No instances of acute liver failure or vanishing bile duct syndrome due to eliglustat have been reported.

Drug Class: Gaucher Disease Agents

Other Drugs in the Class: Miglustat, Glucocerebrosidase (Enzyme Replacement Therapy)

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Eliglustat – Cerdelga®

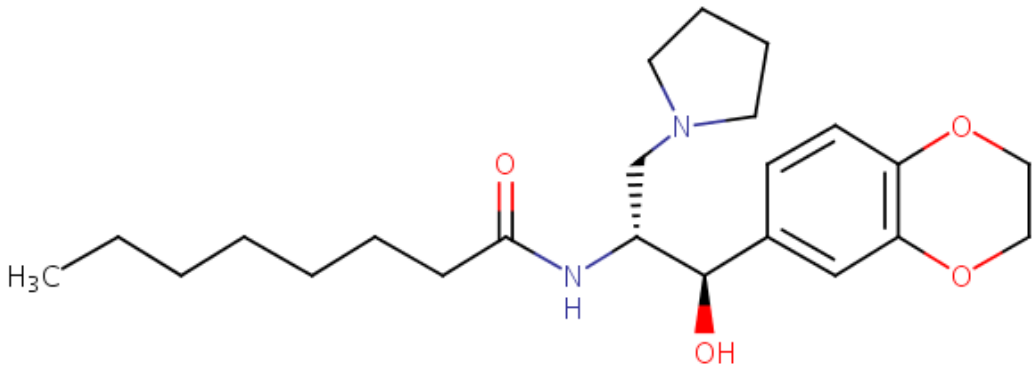
DRUG CLASS

Gaucher Disease Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Eliglustat	491833-29-5	C23-H36-N2-O4	

ANNOTATED BIBLIOGRAPHY

References updated: 05 March 2018

Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 397-416.

(Textbook of pharmacology and therapeutics; eliglustat is not discussed).

McEachern KA, Fung J, Komarnitsky S, Siegel CS, Chuang WL, Hutto E, Shayman JA, et al. A specific and potent inhibitor of glucosylceramide synthase for substrate inhibition therapy of Gaucher disease. Mol Genet Metab 2007; 91: 259-67. PubMed PMID: 17509920.

(Description of a novel glucosylceramide synthase inhibitor [Genz-112738: eliglustat] that inhibits the intracellular enzyme in normal cells, and decreases glucosylceramide accumulation in cells of mouse models of Gaucher disease with no appreciable toxicity providing a substrate inhibition approach to therapy).

Lukina E, Watman N, Arreguin EA, Dragosky M, Iastrebner M, Rosenbaum H, Phillips M, et al. Improvement in hematological, visceral, and skeletal manifestations of Gaucher disease type 1 with oral eliglustat tartrate (Genz-112638) treatment: 2-year results of a phase 2 study. Blood 2010; 116: 4095-8. PubMed PMID: 20713962.

(Among 20 adults with type 1 Gaucher disease treated with eliglustat for at least 2 years, there were clinically important improvements in hemoglobin and platelet count and decreases in spleen and liver size with minimal side effects; no mention of ALT elevations or hepatotoxicity).

Lukina E, Watman N, Dragosky M, Pastores GM, Arreguin EA, Rosenbaum H, Zimran A, et al. Eliglustat, an investigational oral therapy for Gaucher disease type 1: Phase 2 trial results after 4 years of treatment. Blood Cells Mol Dis 2014; 53: 274-6. PubMed PMID: 24835462.

(Among 26 patients with type 1 Gaucher disease treated with eliglustat for up to 4 years, clinical improvements were maintained and there were increasing improvements in bone density; adverse events were largely unrelated to therapy; no mention of ALT elevations or hepatotoxicity).

Eliglustat (Cerdelga)--an oral drug for Gaucher disease. Med Lett Drugs Ther 2015; 57 (1472): e100-1. PubMed PMID: 26147895.

(Concise review of the mechanism of action, clinical efficacy, safety, drug-drug interactions and costs of eliglustat shortly after its approval in the US, mentions side effects of fatigue, headache, nausea, diarrhea and back pain, but does not mention ALT elevations or hepatotoxicity).

Mistry PK, Lukina E, Ben Turkia H, Amato D, Baris H, Dasouki M, Ghosn M, et al. Effect of oral eliglustat on splenomegaly in patients with Gaucher disease type 1: the ENGAGE randomized clinical trial. JAMA 2015; 313: 695-706. PubMed PMID: 25688781.

(Among 40 patients with type 1 Gaucher disease treated with eliglustat or placebo for 9 months, hemoglobin and platelet counts increased and liver and spleen size decreased on eliglustat, but not on placebo and there were no severe adverse events attributable to therapy; no mention of ALT elevations or hepatotoxicity).

Cox TM, Drelichman G, Cravo R, Balwani M, Burrow TA, Martins AM, Lukina E, et al. Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial. Lancet 2015; 385 (9985): 2355-62. PubMed PMID: 25819691.

(Among 106 patients with stable type 1 Gaucher disease on long term enzyme replacement therapy who were switched to eliglustat or maintained on imiglucerase for 12 months, clinical features were stable in both groups, while side effects more frequent with eliglustat included diarrhea, fatigue, nausea, headache, dyspepsia and abdominal pain; no mention of ALT elevations or hepatotoxicity, but one patient developed hepatocellular carcinoma).

Mistry PK, Lukina E, Ben Turkia H, Shankar SP, Baris H, Ghosn M, Mehta A, et al. Outcomes after 18 months of eliglustat therapy in treatment-naïve adults with Gaucher disease type 1: The phase 3 ENGAGE trial. Am J Hematol 2017; 92: 1170-6. PubMed PMID: 28762527.

(Among 40 patients with Gaucher disease treated with eliglustat or placebo for 9 months, spleen size decreased [-28% vs +3%] and platelet counts increased [+32% vs -9%], while there were no serious adverse events in either group and no "clinically meaningful worsening" of routine laboratory test results).

Cox TM, Drelichman G, Cravo R, Balwani M, Burrow TA, Martins AM, Lukina E, et al. Eliglustat maintains long-term clinical stability in patients with Gaucher disease type 1 stabilized on enzyme therapy. Blood 2017; 129: 2375-83. PubMed PMID: 28167660.

(Among 157 patients with Gaucher diseae who were enrolled in a long term extension study after a one year controlled trial of eliglustat vs imiglucerase [Cox 2015], liver and spleen size, hemoglobin and platelet counts were stable for 1-4 years of therapy and there were no serious adverse events or drug discontinuations for ALT elevations or acute hepatotoxicity).

Peterschmitt MJ, Cox GF, Ibrahim J, MacDougall J, Underhill LH, Patel P, Gaemers SJM. A pooled analysis of adverse events in 393 adults with Gaucher disease type 1 from four clinical trials of oral eliglustat: evaluation of frequency, timing, and duration. Blood Cells Mol Dis 2018; 68: 185-91. PubMed PMID: 28126395.

(Among 393 patients with Gaucher disease treated with eliglustat in 4 clinical trials, there were no serious adverse events or drug discontinuations because of ALT elevations or acute liver injury).

Charrow J, Fraga C, Gu X, Ida H, Longo N, Lukina E, Nonino A, Gaemers SJM, Jouvin MH, Li J, Wu Y, Xue Y, Peterschmitt MJ. Once- versus twice-daily dosing of eliglustat in adults with Gaucher disease type 1: The Phase 3, randomized, double-blind EDGE trial. Mol Genet Metab 2018; 123: 347-56. PubMed PMID: 29358012.

(Among 170 adults with Gaucher disease treated with once or twice daily eliglustat for a median of 3.3 years, all deaths [n=2] were unrelated and there were no liver related severe adverse events or liver adverse event related discontinuations).

Zimran A, Belmatoug N, Bembi B, Deegan P, Elstein D, Fernandez-Sasso D, Giraldo P, et al.; GOS Study group. Demographics and patient characteristics of 1209 patients with Gaucher disease: Descriptive analysis from the Gaucher Outcome Survey (GOS). Am J Hematol 2018; 93: 205-12. PubMed PMID: 29090476.

(Summary of clinical features of 1209 patients [95% type 1] enrolled in an international Gaucher disease registry between 2010 and 2017, including 887 [73%] who received at least one therapy, most commonly imiglucerase [66%], velaglucerase [57%], alglucerase [12%], taliglucerase [10%] and miglustat [10%], does not mention eliglustat, adverse events or liver related complications of treatment).