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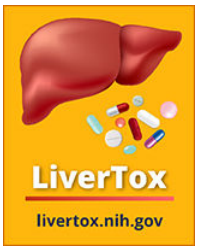


Miglustat

Updated: March 5, 2018.

OVERVIEW

Introduction

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

Background

Miglustat (me' 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 substrate are available, less is available for lysosomal degradation and less glycosylceramide accumulates. Miglustat was shown to decrease the intracellular accumulation of glycosylceramide, the major glycolipid that accumulates in Gaucher disease, in animal models of the genetic disease. In several randomized controlled trials, miglustat was shown to decrease spleen and liver volume and increase hemoglobin and platelet counts in patients with type 1 Gaucher disease. Miglustat 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). Miglustat was approved in the United States in 2003 as oral therapy of type 1 Gaucher Disease in patients who are not eligible for enzyme replacement therapy. Miglustat has also been evaluated in other lysosomal enzyme deficiencies and is approved in Europe, but not the United States as therapy of Niemann–Pick disease, type C. Miglustat is available in tablets of 100 mg under the brand name Zavesca. The usual dose regimen is 100 mg three times daily, but dose adjustments are needed for patients with significant side effects or renal impairment. Side effects are common and can be problematic including diarrhea, weight loss, gastrointestinal upset, nausea and vomiting, anorexia, constipation, headache, tremor, dizziness, weakness, visual problems, dry mouth, paresthesia, peripheral neuropathy, ataxia and memory loss.

Hepatotoxicity

In placebo controlled trials, liver test abnormalities were no more common with miglustat 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 miglustat. However, the total clinical experience with its use has been limited.

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

Mechanism of Injury

The mechanism by which miglustat might cause serum aminotransferase elevations or liver injury is not known. Miglustat 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 miglustat therapy are usually self-limited and do not require dose modification or discontinuation of therapy. No instances of severe hepatitis, acute liver failure or vanishing bile duct syndrome due to miglustat have been reported.

Drug Class: Gaucher Disease Agents

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Miglustat – Generic, Zavesca®

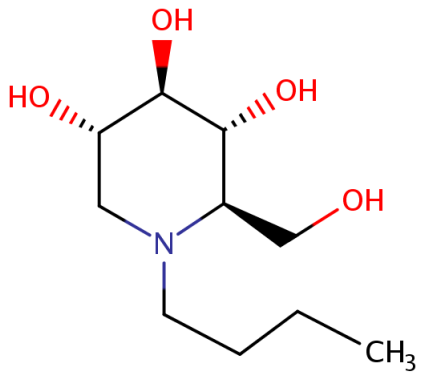
DRUG CLASS

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
Miglustat	72599-27-0	C10-H21-N-O4	

ANNOTATED BIBLIOGRAPHY

References updated: 05 March 2018

Pastores GM, Barnett NL, Kolodny EH. An open-label, noncomparative study of miglustat in type I Gaucher disease: efficacy and tolerability over 24 months of treatment. Clin Ther 2005; 27: 1215-27. PubMed PMID: 16199246.

(Among 10 adults with Gaucher disease treated with miglustat [100 mg thrice daily] for up to 2 years, liver and spleen size decreased, platelet counts rose and hemoglobin levels were stable; while common side effects were abdominal discomfort, diarrhea, flatulence, headache, tremor and paresthesia, there were no serious adverse events and no mention of ALT elevations or hepatotoxicity).

Patterson MC, Vecchio D, Prady H, Abel L, Wraith JE. Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. Lancet Neurol 2007; 6: 765-72. PubMed PMID: 17689147.

(Among 29 patients 12 years of age or older with Niemann-Pick C disease treated with miglustat or placebo for 12 months, miglustat was associated with improvements in eye movements and swallowing, and adverse events included diarrhea, weight loss, abdominal pain, headache, tremor, nausea, fatigue, insomnia and depression; no mention of ALT elevations or hepatotoxicity).

Schiffmann R, Fitzgibbon EJ, Harris C, DeVile C, Davies EH, Abel L, van Schaik IN, et al. Randomized, controlled trial of miglustat in Gaucher's disease type 3. Ann Neurol 2008; 64: 514-22. PubMed PMID: 19067373.

(Among 30 patients with Gaucher disease type 3 treated with miglustat or not, there were no differences in changes in spleen and liver size, and side effects were common including elevations in serum AST in 21% of patients, but no details provided regarding time of onset, duration and severity).

Hollak CE, Hughes D, van Schaik IN, Schwierin B, Bembi B. Miglustat (Zavesca) in type 1 Gaucher disease: 5-year results of a post-authorisation safety surveillance programme. Pharmacoepidemiol Drug Saf 2009; 18: 770-7. PubMed PMID: 19507165.

(A prospective surveillance program with information on 122 patients with type 1 Gaucher disease treated with miglustat for up to 5 years found side effects to include new neurological [19%], bone [9%] and gastrointestinal [3%] disturbances, but did not mention ALT elevations or new onset liver disease).

Shapiro BE, Pastores GM, Gianutsos J, Luzy C, Kolodny EH. Miglustat in late-onset Tay-Sachs disease: a 12-month, randomized, controlled clinical study with 24 months of extended treatment. Genet Med 2009; 11: 425-33. PubMed PMID: 19346952.

(Among 30 patients with late onset Tay-Sachs disease treated with miglustat [200 mg twice daily] or not for 24 months, there were no differences in changes in muscle strength and common adverse events were weight loss, diarrhea, dizziness and paresthesia; "no unexpected abnormal laboratory findings were detected").

Patterson MC, Vecchio D, Jacklin E, Abel L, Chadha-Boreham H, Luzy C, Giorgino R, Wraith JE. Long-term miglustat therapy in children with Niemann-Pick disease type C. J Child Neurol 2010; 25: 300-5. PubMed PMID: 19822772.

(Among 10 children with Niemann-Pick disease type C who were continued on miglustat therapy for 24 months, common side effects were diarrhea, weight loss and tremor, while "there was no pattern of clinically significant abnormal laboratory findings" and mean ALT levels fell by -0.3 U/L).

Guffon N, Bin-Dorel S, Decullier E, Paillet C, Guitton J, Fouilhoux A. Evaluation of miglustat treatment in patients with type III mucopolysaccharidosis: a randomized, double-blind, placebo-controlled study. J Pediatr 2011; 159: 838-844. PubMed PMID: 21658716.

(Among 25 patients with type III mucopolysaccharidosis treated with miglustat or placebo for up to 12 months, there were no improvements in cognitive test results or motor skills with miglustat and rates of side effects [mostly gastrointestinal] were higher; no mention of ALT elevations or hepatotoxicity).

Cox TM, Amato D, Hollak CE, Luzy C, Silkey M, Giorgino R, Steiner RD; Miglustat Maintenance Study Group. Evaluation of miglustat as maintenance therapy after enzyme therapy in adults with stable type 1 Gaucher disease: a prospective, open-label non-inferiority study. Orphanet J Rare Dis 2012; 7: 102 PubMed PMID: 23270487.

(Among 42 patients with Gaucher disease on enzyme replacement therapy treated with miglustat for 2 years, liver volume did not change and side effects were common including diarrhea [71%], tremor [36%] and headache [21%]; no mention of results of laboratory test results).

Kuter DJ, Mehta A, Hollak CE, Giraldo P, Hughes D, Belmatoug N, Brand M, et al. Miglustat therapy in type 1 Gaucher disease: clinical and safety outcomes in a multicenter retrospective cohort study. Blood Cells Mol Dis 2013; 51: 116-24. PubMed PMID: 23683771.

(Among 115 patients with type 1 Gaucher disease treated with miglustat in clinical practice, 49 [43%] stopped treatment mostly because of adverse events; no mention of liver related adverse events or ALT elevations).

Chien YH, Peng SF, Yang CC, Lee NC, Tsai LK, Huang AC, Su SC, et al. Long-term efficacy of miglustat in paediatric patients with Niemann-Pick disease type C. J Inherit Metab Dis 2013; 36: 129-37. PubMed PMID: 22476655.

(Among 5 children with Niemann-Pick disease type C treated with miglustat for up to 6 years, most children had stable disease and "no safety and tolerability issues were reported").

Patterson MC, Mengel E, Vanier MT, Schwierin B, Muller A, Cornelisse P, Pineda M; NPC Registry investigators. Stable or improved neurological manifestations during miglustat therapy in patients from the international disease registry for Niemann-Pick disease type C: an observational cohort study. Orphanet J Rare Dis 2015; 10: 65. PubMed PMID: 26017010.

(Among 92 European patients with Neimann-Pick disease type C treated with continuous miglustat and enrolled in an international registry, 70% were categorized as improved or stable and "no unexpected safety findings were identified").

Brand M, Muller A, Alsop J, van Schaik IN, Bembi B, Hughes D. Results from a 9-year Intensive Safety Surveillance Scheme (IS(3)) in miglustat (Zavesca(®))-treated patients. Pharmacoepidemiol Drug Saf 2015; 24: 329-33. PubMed PMID: 25656910.

(During 9 years of an intensive safety surveillance scheme which enrolled 407 patients [half with Gaucher disease] treated with miglustat for up to 9 years, 51% discontinued therapy, largely because of adverse events usually gastrointestinal [diarrhea, weight loss]; no mention of ALT elevations or hepatotoxicty]).

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 [another oral glucosylceramide synthase inhibitor] 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).

Giraldo P, Andrade-Campos M, Alfonso P, Irun P, Atutxa K, Acedo A, Barez A, et al. Twelve years of experience with miglustat in the treatment of type 1 Gaucher disease: The Spanish ZAGAL project. Blood Cells Mol Dis 2016 Oct 24. [Epub ahead of print] PubMed PMID: 27836529.

(Among 63 Spanish patients with type 1 Gaucher disease treated enzyme replacement therapy and then switched to miglustat and followed for up to 10 years, blood counts, liver volume and spleen sizes remained stable, while side effects included transient diarrhea in 40%, mild temporary tremor in 60% and nonprogressive neuropathy in 3%; no mention of ALT elevations or hepatotoxicity).

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 adverse events or liver related complications of treatment).