



National Tay-Sachs &
Allied Diseases Association

Use of miglustat in GM1 and GM2 Gangliosidoses

The following information is for individuals living with rare diseases and their healthcare providers (HCPs) considering off-label use of miglustat for GM1 and GM2 gangliosidoses (Tay-Sachs and Sandhoff diseases). This document is not intended to provide medical advice; individuals interested in using miglustat off-label should discuss this with their HCPs. This information is intended for affected individuals living in the US; the approval status of medications may vary by country. Countries outside of the US may have regulations or processes in place to access medications via off-label drug use (OLDU) as well.

NTSAD does not advocate for or against OLDU of specific drugs for any individuals.

- Background
 - Additional drug names: *N*-butyl-deoxynojirimycin (NB-DNJ); OGT-918 and SC-48334 (compound names during clinical development).
 - Brand names: Zavesca[®], Brazevas[®], Opfolda[®], Yargesa[®], miglustat, miglustat dipharma, miglustat Gen Orph.
 - Generic name: miglustat. More synonyms:
<https://go.drugbank.com/drugs/DB00419>;
<https://pubchem.ncbi.nlm.nih.gov/compound/Miglustat>.
 - Mechanism(s) of Action: This small-molecule iminosugar binds to several glycosidic enzymes throughout the body with varying affinities, resulting in distinct mechanisms of action with both intended (on-target) therapeutic benefits and unintended (off-target) side effects. Miglustat can function as a substrate reduction therapy (SRT), an anti-inflammatory agent, and a pharmacological chaperone.
 - Miglustat is best known as a substrate reduction therapy that prevents the accumulation of lysosomal glycosphingolipids (including GM1 and GM2) in lysosomal storage disorders. By partially inhibiting glucosylceramide (glucocerebroside) synthase, the first committed enzyme in glycosphingolipid synthesis, miglustat achieves a better balance between lower synthesis and impaired degradation, resulting in reduced lysosomal storage of glycosphingolipids.

- Less well-known is miglustat's ability to potently inhibit non-lysosomal β -glucosidase 2 (GBA2), which breaks down glucosylceramide located at the plasma membrane (outer layer of the cells) and endoplasmic reticulum (a network of membranes within a cell that transports proteins and other molecules and is involved in the synthesis of lipids and proteins). The GBA2 is highly expressed in the brain. This seemingly paradoxical increase in extralysosomal glucosylceramide is believed to be beneficial in several lysosomal storage disorders by preventing the formation of bioactive, potentially toxic metabolites (e.g., ceramide and lyso-GL1) that can trigger immune activation, inflammation, and neuronal toxicity. Miglustat's ability to clear accumulated glycosphingolipids in lysosomes and reduce neuroinflammation likely acts in a complementary manner to slow neurodegeneration.
- Miglustat has also been used as a pharmacological chaperone (enzyme stabilizer) to prevent the inactivation of cipa glucosidase alfa (Pombiliti[®]) in the blood during intravenous administration for the treatment of late-onset Pompe disease.
- **Safety:** Miglustat interferes with the digestion of carbohydrates by inhibiting small intestine enzymes that break down sugars, known as disaccharidases, mainly sucrase and maltase, and, to a lesser extent, isomaltase and lactase. Increased disaccharide levels in the gut lead to osmotic malabsorption and the fermentation of undigested disaccharides in the colon, producing common side effects of diarrhea, bloating, flatulence, and weight loss, and, less commonly, abdominal discomfort, nausea, and dyspepsia. These side effects can be managed by dietary modification (low-carbohydrate intake), anti-diarrhea agents (e.g., loperamide), gradual dose escalation (to improve tolerability), and administration between meals (to mitigate disaccharidase inhibition). Gastrointestinal problems generally subside over several weeks with these measures. Miglustat can also cause neurological side effects, including tremor, peripheral neuropathy, unsteady gait/dizziness, and headache. Their cause is unknown but may be due to the depletion of glycosphingolipids required for normal neuronal function or off-target effects in other glycosidic pathways. Neurological side effects are managed by reducing the dose or discontinuing miglustat. Mechanisms of action are reviewed in Cox, 2005; Pastores, 2006; Loberto *et al*, 2014; Parenti *et al*, 2014.

- **Approvals and Off-Label Use**

- Zavesca was approved to treat adult patients with mild to moderate type I Gaucher disease (GD1) who cannot receive enzyme replacement therapy, first by EMA (EU) in 2002 and then by FDA (US) in 2003.
 - The pivotal study was open-label and uncontrolled, enrolling 28 patients with mild-to-moderate GD1 who received miglustat 100 mg PO three times daily for 12 months. Compared with baseline values, miglustat led to significant reductions in spleen and liver volumes and non-significant increases in hemoglobin concentration and platelet count (Cox *et al*, 2000). In a 24-month extension study, all four endpoints continued to improve (Elstein *et al*, 2004). The most common adverse events were diarrhea, flatulence, and weight loss. Some patients experienced mild, generally reversible tremor or peripheral neuropathy.
 - A randomized (1:1:1 to miglustat, imiglucerase, or miglustat plus imiglucerase), active-controlled, 6-month switch study evaluated miglustat 100 mg PO three times daily as a maintenance therapy in 36 patients with GD1 who had been receiving Cerezyme[®] (imiglucerase) for at least 2 years. This was followed by an open-label, 6-month extension study in which all patients received miglustat. After 6 months, there was a significant reduction in platelet count among patients treated with miglustat compared with those treated with imiglucerase. There was a significant decrease in platelet counts from Month 6 to Month 12 in the group that switched from imiglucerase to miglustat, and a continued decrease in platelet counts in the group that continued to receive miglustat alone. (Zavesca prescribing information, 2022)
- Miglustat was approved to treat the neurological manifestations in Niemann-Pick disease type C (NPC), initially as a monotherapy (Zavesca) by the EMA (EU) in 2009, and later in combination with arimoclomol (Miplyffa, Zevra Therapeutics) by the FDA in 2024.
- Miglustat (Opfolda) was approved by the FDA and EMA in 2023 in combination with cipaglucosidase alfa (Pombiliti, Amicus Therapeutics) for the treatment of adults with late-onset Pompe disease who are not improving on current ERT.
- Miglustat has been used off-label as a monotherapy in several childhood-onset neurodegenerative lysosomal storage disorders, including type III Gaucher disease (GD3), Niemann-Pick disease type C (NPC), Batten disease (juvenile neuronal ceroid lipofuscinosis caused by the *CLN3* gene), and GM1 and GM2 gangliosidoses.

- **Non-clinical Studies in GM2 Gangliosidosis**
 - Miglustat reduces GM2 levels in the *Hexa*^{-/-} mouse model of Tay-Sachs disease, a type of GM2 gangliosidosis (Platt *et al*, 1997). However, this mouse model accumulates only a modest amount of GM2 that falls below the threshold for neurodegeneration.
 - A study in the *Hexb*^{-/-} mouse model of Sandhoff disease, which does experience neurodegeneration, showed that miglustat reduced GM2 accumulation and modestly delayed neurodegeneration (Jeyakumar *et al*, 1999). Improved motor function and a 40% increase in lifespan were observed when mice were treated in the early pre-symptomatic phase (<6 weeks of age), but not at the late presymptomatic phase (11 weeks of age), suggesting a treatment window after which disease progression is irreversible.
 - A later study in *Hexb*^{-/-} mice treated with miglustat showed slowing of glycosphingolipid accumulation in the CNS, which delayed the onset of neuroinflammation and disease pathogenesis (Jeyakumar *et al*, 2003).

- **Non-clinical Studies in GM1 Gangliosidosis**
 - In the *β-gal*^{-/-} mouse model of GM1 gangliosidosis treated pre-symptomatically at 3-4 weeks of age, miglustat reduced brain GM1 and GA levels and normalized the endocytic recycling of glycosphingolipids (Eliot-Smith *et al*, 2008). Reduction in microglial activation (neuroinflammation) was also observed. Unlike untreated mice, miglustat-treated mice maintained rearing activity behavior throughout their lifespan. However, survival was not extended, which was attributed to the exacerbation of underlying GI disease by miglustat, leading to rectal prolapse and necessitating humane euthanasia.

- **Available Clinical Data in GM2 gangliosidosis**
 - A randomized (2:1, miglustat:no miglustat), open-label, multicenter clinical trial evaluated miglustat 300 mg PO qd in 30 adults with late-onset Tay-Sachs disease after 12 months, and after a 24-month extension in which all patients received miglustat (Shapiro *et al*, 2012). The primary endpoint, muscle and grip strength, decreased similarly in both groups during the study, and no differences were observed in secondary efficacy measures of gait, balance, and overall disability. The most common side effects were diarrhea and weight loss.
 - Mansouri summarized the experience with miglustat treatment in 54 patients with GM2 gangliosidosis from the medical literature (Mansouri *et al*, 2023). The review included patients with infantile, late-infantile,

juvenile, and adult-onset GM2 gangliosidosis who were evaluated in five clinical trials, four case reports, and one case series. No consistent clinical benefit was observed. Interpretation of the results is limited by an insufficient sample size, a short follow-up period, and the short-term survival of infantile patients. The most common side effects of miglustat were gastrointestinal, including diarrhea, weight loss, flatulence, abdominal pain, and nausea/vomiting, and were consistent with the safety profile in GD1.

- **Available Clinical Data in GM1 Gangliosidosis**

- No formal clinical trials of miglustat have been performed in patients with GM1 gangliosidosis. Two small case series have been published (Deodato *et al*, 2017; Fischetto *et al*, 2020).
- Three patients with GM1 gangliosidosis (two juvenile-onset and one adult-onset patients) were treated off-label with a high dose of miglustat (600 mg PO daily) at 10-28 years of age and assessed periodically over 3-11 years (Deodato *et al*, 2017). All three had severe neurological impairment at baseline and showed modest, sustained gains with treatment. The two juvenile-onset patients regained the ability to walk a few meters without assistance and showed increased alertness and vocalization. The adult patient showed improved ambulation (6-minute walk test) and speech fluency.
- Four patients with juvenile-onset GM1 gangliosidosis were treated off-label with miglustat (240 mg to 300 mg PO daily) beginning at 20 months to 10.5 years of age and assessed periodically for 3-7 years (Fischetto *et al*, 2020). Three of the four patients showed stabilization or slowing of neurological disease progression.

- **On-label Recommended Dosing (per Package Insert)**

- Recommendations for Zavesca (miglustat) capsules are available here: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021348s0161bl.pdf. This US prescribing information states that the recommended total daily dose of Zavesca in adults with GD1 is 300 mg PO/day, taken orally as 100 mg capsules PO three times a day at regular intervals. In some patients, it may be necessary to reduce the dose to one 100 mg capsule PO once or twice daily due to adverse reactions, such as tremor or diarrhea. The starting daily dose is reduced in patients with mild (200 mg) or moderate (100 mg) renal impairment and is not recommended in patients with severe renal impairment. Note warnings and precautions for peripheral neuropathy (3%), tremor (30%), diarrhea (85%) and weight loss

(65%) in GD1 patients, and reductions in platelet counts (40%) in non-GD indications.

- In Europe, where Zavesca is approved for Niemann-Pick type C, the approved dose is 200 mg PO three times daily for patients ages 12 years and over; dosing is based on body surface area for children under 12 years of age.
 - In a study of juvenile GM2 gangliosidosis patients, the initial dose of 200 mg PO TID was better tolerated in younger children with the early-onset juvenile clinical form than in those with the late-juvenile form, who had greater self- and independent dietary choices. In the latter subgroup of late-juvenile GM2 gangliosidosis, the 100 mg PO three times a day dose was better tolerated (Maegawa *et al*, 2009).
 - The most common adverse reactions (incidence $\geq 5\%$) are: diarrhea, weight loss, stomach pain, gas, nausea and vomiting headache including migraine, tremor, leg cramps, dizziness, weakness, vision problems, thrombocytopenia, muscle cramps, back pain, constipation, dry mouth, heaviness in arms and legs, memory loss, unsteady walking, anorexia, indigestion, paresthesia, stomach bloating, stomach pain not related to food, and menstrual changes.
 - Zavesca has not been studied in children with GD1 and is not recommended for use in patients below the age of 18.
 - Zavesca may cause fetal harm based on animal data, and breastfeeding is not recommended while taking Zavesca.
-
- This document provides information and references on miglustat. For general information on off-label drug use, please see our general guidelines document. For information on additional off-label drugs, please see our other drug-specific documents, which are available on NTSAD's website.
 - This document was organized by the National Tay-Sachs & Allied Diseases Association (NTSAD) Research Committee working group. It was authored by Gerald F. Cox, MD, PhD, from the NTSAD Research Committee with input from other NTSAD Research Committee members and members of the NTSAD Scientific Advisory Committee.
 - If you have additional questions, please contact research@ntsad.org.

References:

- 1) DrugBank: <https://go.drugbank.com/drugs/DB00419>
- 2) PubChem: <https://pubchem.ncbi.nlm.nih.gov/compound/Miglustat>

- 3) Cox TM. Substrate reduction therapy for lysosomal storage diseases. *Acta Paediatr Suppl* 2005;94:69-75. PMID: 1589571
- 4) Pastores GM. Miglustat: Substrate reduction therapy for lysosomal storage disorders associated with primary central nervous system involvement. *Recent Pat CNS Drug Discov* 2006;1:77-82. PMID: 18221193
- 5) Loberto N, Tebon, I Lampronti, *et al.* GBA2-encoded β -glucosidase activity is involved in the inflammatory response to *Pseudomonas aeruginosa*. *PloS One* 2014;9:e104763. PMID: 25141135
- 6) Parenti G, S Fecarotta, G la Marca, *et al.* A chaperone enhances blood α -glucosidase activity in Pompe disease patients treated with enzyme replacement therapy. *Mol Ther* 2014;22:2004-2012. PMID: 25052852
- 7) Cox TM, R Lachmann, C Hollak, *et al.* Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. *Lancet* 2000;355:481-1485. PMID: 10801168
- 8) Elstein D, C Hollak, JMFG Aerts, *et al.* Sustained therapeutic effects of oral miglustat (Zavesca, N-butyldeoxynojirimycin, OGT918) in type I Gaucher disease. *J Inherit Metab Dis* 2004;27:757-766. PMID: 15505381
- 9) ZAVESCA (miglustat) prescribing information. US FDA. Initial approval: 2003. Revised label 12/2022
- 10) MYPLIFFA (arimoclomol) prescribing information. US FDA. Initial approval. 2024. Revised label 9/2024
- 11) OPFOLDA (miglustat) prescribing information. US FDA. Initial approval: 2003. Revised label 9/2023
- 12) Platt FM, GR Neises, G Reinkensmeier, *et al.* Prevention of lysosomal storage in Tay-Sachs mice treated with N-butyldeoxynojirimycin. *Science* 1997;276:428-431. PMID: 9103204
- 13) Jeyakumar M, TD Butters, M Cortina-Borja. Delayed symptom onset and increased life expectancy in Sandhoff disease mice treated with N-butyldeoxynojirimycin. *Proc Nat Acad Sci* 1999;96:6388-6393. PMID: 10339597
- 14) Jeyakumar M, R Thomas, E Eliot-Smith. Central nervous system inflammation is a hallmark of pathogenesis in mouse models of GM1 and GM2 gangliosidosis. *Brain* 2003;126:974-987. PMID: 12615653
- 15) Eliot-Smith E, AO Speak, E Loyd-Evans, *et al.* Beneficial effects of miglustat in a mouse model of GM1 gangliosidosis. *Mol Genet Metab* 2008;94:204-211. PMID: 18387328
- 16) Shapiro BE, Pastores GM, J Gianutsos, *et al.* Miglustat in late-onset Tay-Sachs disease: a 12-month, randomized, controlled clinical study with 24 months of extended treatment. *Genet Med* 2009;11:425-433. PMID: 19346952

- 17) Mansouri V, AR Tavasoli, M Khodarahrm, *et al.* Efficacy and safety of miglustat in the treatment of GM2 gangliosidosis: A systematic review. *Eur J Neurol* 2023;30;2919-2945. PMID: 37209042
- 18) Deodato F, E Procopio, A Rampazzo, *et al.* The treatment of juvenile/adult GM1-gangliosidosis with miglustat may reverse disease progression. *Metab Brain Dis* 2017;32:1529-1536. PMID: 28577204
- 19) Fischetto R, V Palladino, MM Mancardi, *et al.* Substrate reduction therapy with miglustat in pediatric patients with type 2 GM1 gangliosidosis delays neurologic involvement: A multicenter experience. *Mol Genet Genomic Med* 2020;8:1371. PMID: 32779865
- 20)EMA website on Zavesca:
<https://www.ema.europa.eu/en/medicines/human/EPAR/zavesca>
- 21)Maegawa, GH, BL Banwell, S Blaser, *et al.* Substrate reduction therapy in juvenile GM2 gangliosidosis. *Mol Genet Metab*, 2009;98:2 PMID: 19595619