



National Tay-Sachs &
Allied Diseases Association

Use of Riluzole in GM2 Gangliosidoses

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

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

- Background
 - Additional drug names: Rilutek, Exservan, Tiglutik, 2-amino-6-(trifluoromethoxy)benzothiazole. A full list of synonyms is available at: <https://pubchem.ncbi.nlm.nih.gov/compound/5070>; <https://go.drugbank.com/drugs/DB00740>. The drug class is benzothiazoles.
 - Riluzole is a small molecule drug that has three main pharmacological properties: i) It is a glutamate (excitatory neurotransmitter) antagonist (i.e. glutamate release inhibitor); ii) it causes inactivation of voltage-dependent sodium channels, which are regulators of neuronal firing in the deep cerebellar neurons; and iii) it has the ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors (Doble, 1996; <https://pubchem.ncbi.nlm.nih.gov/compound/5070>; <https://go.drugbank.com/drugs/DB00740>). It may act as a general neuroprotective agent with anticonvulsant properties due to one or more of its above-described pharmacological properties. Hyperexcitability of the deep cerebellar nuclei may contribute to dysfunction in cerebellar diseases, making them a potential therapeutic target.
 - The FDA approved this drug for amyotrophic lateral sclerosis (ALS) in 1995. It was the first drug approved for ALS in the United States based on the clinical studies showing riluzole extends survival and/or time to tracheostomy in ALS patients. Riluzole tablets are marketed as Rilutek and other names due to additional formulations, and although it is not a

cure, it is thought to extend survival, with a delay in median time to death, time to tracheostomy, with a delay in onset of ventilator-dependence in individuals with ALS (Hinchcliffe & Smith, 2017; Miller *et al*, 2011).

- Riluzole has also shown potential efficacy in a small study of patients with mixed ataxia (Romano *et al*, 2015). Romano *et al*. performed a randomized, double blind, placebo-controlled study of riluzole in a mixed ataxia cohort (2:1 spinocerebellar ataxia: Friedreich's ataxia). There were rare adverse events (AE); two patients in the riluzole group had elevated LFTs (<2x upper limit of normal), in keeping with the previous known side-effect profile (Bensimon and Doble, 2004), and there were otherwise sporadic, mild AEs and no serious AEs (Romano *et al*, 2015). In this study, primary endpoint was 50% with at least a 1-point improvement in the Scale for the Assessment and Rating of Ataxia (SARA) score at 12 months in the treated vs. 11% in the placebo group (p=0.002), with a mean difference in change in SARA at 3 months of -1.50 and -2.68 at 12 months (p<0.05) compared with placebo, with a 1 point mean decrease in SARA in the riluzole group, which was maintained at 3 and 12 months (Romano, 2015). A similar drug, troriluzole (a pro-drug of riluzole) is currently being studied in the spinocerebellar ataxias (Biohaven). <https://www.clinicaltrials.gov/study/NCT03701399>
- Riluzole has been studied in POLR3-related leukodystrophy, a group of rare neurodegenerative diseases caused by biallelic pathogenic variants in genes encoding Pol III subunits. It has been shown to partly correct the defects in Pol III assembly that are found in a POLR3B subunit with the R103H variant (mutation known to be causative for POLR3-related leukodystrophy), and thus it is proposed to be useful to treat some of the POLR3-related leukodystrophies that are caused by assembly defects (Pinard *et al*, 2022). There is also data regarding the use of riluzole in Niemann-Pick disease, type C1, a lysosomal storage disorder (Cognoux *et al*, 2021), which is described in more detail below.
- Studies have also demonstrated possible efficacy of riluzole in psychiatric disorders, in adult and children, including severe mood, anxiety and impulsive disorders (reviewed in Zarate and Manji, 2008; Grant *et al*, 2010), including obsessive compulsive disorder (Grant *et al*, 2010), depression (Salardini *et al*, 2016) as well as possibly in the treatment of negative symptoms in patients with chronic schizophrenia (Farokhnia *et al*, 2014).
- Riluzole has been studied in multiple other disorders. It is thought to be effective as an anti-neoplastic drug in many types of cancers, including skin, breast, pancreas, colon, liver, bone, brain, lung, and nasopharynx,

and seems to block cell proliferation and/or induce cell death (reviewed in Blyufer *et al*, 2021; Biechele *et al*, 2010).

- Approved uses
 - Riluzole is currently approved for use only in ALS. Since the initial approval of riluzole in tablet form (Rilutek) in 1995, the FDA has approved several additional formulations, including a thickened liquid form called Tiglutik and an oral film formulation called Exservan for those with swallowing difficulties.

- Available data in GM2 gangliosidoses and/or other lysosomal storage disorders
 - Currently, we do not find any published literature describing the use of riluzole in GM2 gangliosidoses, either in animal models or patients.
 - Riluzole has been studied in Niemann-Pick disease, type C1, another lysosomal storage disorder with CNS involvement. In a mutant mouse model of Niemann-Pick disease, type C1 (Npc1^{-/-}), riluzole treatment delayed disease progression and increased survival by 12%. It was hypothesized that, because glutamate neurotoxicity plays a role in Niemann-Pick disease, type C1 disease progression, riluzole would be effective based on its actions as a glutamate receptor antagonist, inhibiting postsynaptic glutamate receptor signaling and reducing glutamate release (Cougnoux *et al*, 2021).
 - While this is unpublished, we are anecdotally aware of at least one individual with late-onset Tay-Sachs (LOTS), who was prescribed riluzole 50mg PO (oral) BID. Patient reported remarkable improvements in speech.
 - Neurodegenerative diseases, like the GM2 gangliosidoses, GM1 gangliosidosis, Niemann-Pick disease, and ALS, share common pathophysiologic features. Thus, riluzole may have the potential to treat multiple lysosomal diseases with neurodegeneration, yet this remains to be determined.

- On-label recommended dosing (per labeling information)
 - Recommendations for Rilutek (riluzole) tablets are available here: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020599s011s012lbl.pdf. The recommended dose for Rilutek is 50 mg PO every 12 hours. No increased benefit is expected from higher daily doses, but adverse events are more likely. Exservan (riluzole) oral film recommendations are available here: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212640s0011

bl.pdf. The recommended dosage for Exservan is 50 mg taken orally twice daily. Recommendations for Tiglutik (riluzole) oral suspension are here: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/209080s0051bl.pdf. The recommended dose for Tiglutik is 50 mg (10 mL) taken orally or via Percutaneous Endoscopic Gastrostomy (PEG-tubes) every 12 hours.

- All 3 formulations should be taken at least 1 hour before or 2 hours after a meal.
 - Common adverse reactions described in the three labeling documents above include: asthenia, nausea, dizziness, decreased lung function, diarrhea, abdominal pain, pneumonia, vomiting, vertigo, circumoral paresthesia, anorexia, and somnolence. Dose-related adverse reactions included asthenia, nausea, dizziness, diarrhea, anorexia, vertigo, somnolence, and circumoral paresthesia. The most commonly reported adverse reactions in those patients who discontinued riluzole due to adverse events were: nausea, abdominal pain, constipation, and ALT elevations.
 - In addition to indications, usage, and adverse reactions, the three labeling documents also describe warnings and precautions, metabolism and elimination, clinical studies, drug interactions, clinical pharmacology, and more. Additional safety, toxicity, and interaction data are also available at <https://pubchem.ncbi.nlm.nih.gov/compound/5070> and <https://go.drugbank.com/drugs/DB00740>.
- This document provides information and references on riluzole. For general information on OLDU, please see our general guidelines document, “Off-label Drug Use General Information,” available at <https://ntsad.org/resources-for-professionals/off-label-drug-information/>. For information on additional off-label drugs, please refer to our other drug-specific documents, also available on the NTSAD website at: <https://ntsad.org/resources-for-professionals/off-label-drug-information/>.
 - This document was organized by the National Tay-Sachs & Allied Diseases Association (NTSAD) Research Committee working group. It was authored by Cynthia Perreault-Micale, PhD, and Valerie Greger, PhD, from NTSAD, 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.

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