**Letter of Medical Necessity Template Guidance for Lembaz™ (adrabetadex) Injection 900 mg/4.5 mL, for Intrathecal Use**

The following document includes possible content to be used as a **letter of medical necessity** in support of a patient receiving Lembaz™ (adrabetadex) for the treatment of Niemann-Pick disease, type C, with neurological manifestations that started at less than 6 years of age. This information does not constitute medical or legal advice and does not guarantee reimbursement for coverage. It is not intended to influence, or be a substitute for, the independent clinical decision-making of the prescribing healthcare professional. (Note: the Important Safety Information does not need to be included as part of your letter and is intended for your information only.)

This sample letter is intended to provide templated language and be used as a guide. Edits should be made to address the specific needs of your patient and to outline the reason(s) why Lembaz merits coverage as an appropriate treatment option for your patient. You should always include pertinent clinical information that supports your decision to prescribe Lembaz.

Please see below for considerations when writing a letter of medical necessity:

- Review the health plan medical policy criteria and point out the criteria that your patient meets
- As applicable, explain why exclusionary criteria listed in the medical policy do not apply to your patient
- Provide background on your patient's condition and clearly state your patient's individual circumstances to justify why Lembaz is the appropriate choice
- Provide clinical justification and include copies of relevant clinical data to support your decision (chart notes, genetic testing results, etc)
- Submit the letter as required by the health plan and state guidelines. It is important that you understand the process for each health plan, including how to submit the request (eg, fax, phone, email, the company's website) as well as how and when the decision will be communicated
- Track the status of your request and follow up with the health plan as needed

**Data context and limitations:** This sample letter includes data from the Lembaz Prescribing Information and supportive analyses not included in the Prescribing Information. Supportive findings should be considered in the context of the respective study designs and limitations.

**Please see Important Safety Information on the next page and in the full Prescribing Information, including Boxed WARNING.**

**Indication and Important Safety Information**

INDICATION

LEMBAZ™ (adrabetadex) is indicated to reduce the risk of mortality in adult and pediatric patients, who weigh 7 kg or greater, with Niemann-Pick disease type C (NPC) with neurological manifestations that started at less than 6 years of age.

**IMPORTANT SAFETY INFORMATION**

**WARNING: HEARING IMPAIRMENT INCLUDING PERMANENT HEARING LOSS**

**Treatment with LEMBAZ has resulted in permanent hearing impairment.**

- **Prior to LEMBAZ use, perform a comprehensive audiology evaluation (e.g., pure tone audiometry, speech recognition, tympanometry) to establish baseline hearing levels.**
- **During LEMBAZ treatment, modify LEMBAZ dosage based on comprehensive audiology evaluations as follows:**
  - **To determine the subsequent dosage level, repeat comprehensive audiology evaluation 1 to 2 weeks after the first LEMBAZ dose at each dosage level but before the next dose, and then 1 to 2 weeks after the second LEMBAZ dose at each dosage level but before the next dose.**
  - **When a patient remains at the same LEMBAZ dosage level for 2 consecutive doses or has reached the maximum dosage, perform comprehensive audiology evaluations at one-month intervals until 3 consecutive, stable audiology results are obtained, and then repeat the comprehensive audiology evaluations every 12 months.**

**WARNINGS AND PRECAUTIONS**

**Hearing Impairment Including Permanent Hearing Loss:** LEMBAZ-treated patients experienced permanent hearing impairment that ranged from mild to profound hearing loss, including in some patients with normal hearing at baseline. Do not increase the dosage if audiology results show hearing impairment below 4,000 Hz that exceeds the thresholds defined in the full Prescribing Information. In patients with LEMBAZ-associated hearing impairment, data are insufficient to determine whether continuing or lowering the dose affects the risk of further hearing impairment.

**Ataxia:** LEMBAZ can cause ataxia, including fall, abnormal gait and/or coordination, dizziness, and hypotonia. This may occur shortly after a dose, typically in the first few days. Severe ataxia requiring hospitalization has occurred. Ataxia may be more severe at higher doses. Monitor patients for ataxia severity and consider reducing the dosage to reduce ataxia severity.

**Please see additional Important Safety Information on the next page and the full Prescribing Information, including Boxed WARNING.**

**IMPORTANT SAFETY INFORMATION (cont'd)**

**WARNINGS AND PRECAUTIONS (cont'd)**

**Fatigue:** LEMBAZ can cause fatigue, including asthenia, fatigue, malaise, and somnolence. This may occur shortly after a dose, typically in the first few days. Severe fatigue requiring hospitalization has occurred. Fatigue may be more severe at higher doses. Monitor patients for fatigue severity and consider reducing the dosage to reduce fatigue severity.

**ADVERSE REACTIONS**

The most common adverse reactions (reported in ≥25% of patients) were hearing impairment, ataxia, fatigue, vomiting, back pain, headache, pyrexia, diarrhea, nausea, and cough.

**To report SUSPECTED ADVERSE REACTIONS, contact Mandos, LLC at 1-844-237-3600 or FDA at 1-800-FDA-1088 or** www.fda.gov/medwatch**.**

Administer LEMBAZ intrathecally by, or under the supervision of, a healthcare provider experienced in performing lumbar punctures.

**Please see the full Prescribing Information, including Boxed WARNING.**

**Sample Letter of Medical Necessity**

[Physician letterhead]

[Date]
Attn: [Health plan contact name]
[Health plan name]
[Address]
[City, state, ZIP code]

Patient name: [First and last name]
Date of birth: [Patient date of birth]
Policy number: [Number]
Group number: [Number]
[Claim number: Number if relevant to request]

RE: Lembaz™ (adrabetadex) Expedited/Urgent Approval Request

Dear [Health plan contact name]:

I am writing this letter on behalf of the above-mentioned patient, [Patient name], to document the medical necessity of [initiating/continuing] treatment with Lembaz™ (adrabetadex), a US Food and Drug Administration (FDA)–approved therapy indicated to reduce the risk of mortality in adult and pediatric patients, who weigh 7 kg or greater, with Niemann-Pick disease type C (NPC), with neurological manifestations that started at less than 6 years of age.

I am a board-certified [field of certification] ([National Provider Identifier]) and at our institution, [name of institution], our teams have [#] years of experience caring for patients with NPC. Lembaz is **medically necessary** and withholding or delaying this critical treatment could cause increased morbidity and mortality. I am requesting that this matter be reviewed on an **expedited/urgent basis**.

To provide background, NPC is a rare, progressive, neurodegenerative, autosomal recessive disorder caused by impaired cholesterol trafficking, resulting in cholesterol accumulation and downstream cellular dysfunction which ultimately leads to premature death.[1-4] Any delay in treatment could seriously jeopardize my patient's life, health, or ability to maintain function, and result in irreversible clinical decline. Without intervention that addresses the underlying pathophysiology of the disease, patients with infantile-onset NPC (I-NPC) face a mean survival of approximately 6 to 13 years from birth, depending on disease onset subtype.[5] Every day of delayed access to therapy represents continued neuronal loss and damage that is irreversible once incurred. Delayed access to therapy is not a neutral event; each day of untreated disease permits neuronal loss that is irreversible, compounding long-term clinical burden.[6]

**Summary of Patient's Medical History**

[HCP to outline information about the patient's medical history, which may include:]

- E75.242 Niemann-Pick disease type C with confirmed genetic testing (if applicable), this patient has been diagnosed with I-NPC. Please see additional documentation
- Previous treatments/therapies (if any) and patient's response to these treatments/therapies, including reasons for failure, discontinuation, or contraindication (if available)
- Without treatment, I-NPC causes progressive and irreversible loss of neuronal function.[6] Initiation of Lembaz is medically necessary to help preserve [Patient name]'s existing functional abilities, prevent further irreversible decline, and improve survival

[**Expanded Access Program (EAP) Continuation**]

- [If the request is for continuation of [Patient's Name]'s treatment that has been a part of an EAP program through an IND at Dr. Elizabeth Berry-Kravis at Rush University Medical Center, include the follow:] They have been on treatment for [XX years/months] and because of this treatment [insert clinical rationale, eg, improvement or slowing of symptoms]. Attached is [medical documentation of positive response to treatment]. **Interrupting the treatment could have serious consequences, including medical decline and premature mortality.]**

[HCP to outline any relevant clinical data on Lembaz—see example in appendix]

In summary, given the patient's history, current condition, and reduced life expectancy for patients with NPC, the available data demonstrating the effects of Lembaz on survival in patients with NPC, I believe that treatment is warranted, appropriate, and medically necessary and should be covered and reimbursed. The totality of the data available to date supports the potential benefit of [treatment/continuing treatment] with Lembaz.

Please do not hesitate to contact me for any additional information. I look forward to receiving your timely response and approval of this claim.

Sincerely,
[Physician name, National Provider Identification]
[Office phone number]
[Email]

[Attachment checklist:]
- [Copy patient's health plan card(s)
- Clinical supporting documents: Lembaz Prescribing Information; Clinical practice guidelines (such as the 2025 Consensus Clinical Management Guidelines for Niemann-Pick Disease Type C) or peer-reviewed literature
- Relevant information such as chart notes, laboratory results, and functional assessment results; original claim form; and previous communications with the health plan/denial letters (if relevant)]

**[Appendix (optional)]**

**Clinical Evidence Reference**

[The clinical data summaries in the sections below (Survival Benefit, Importance of Early Intervention, Concomitant Therapy) are compiled by Beren Therapeutics as a reference resource based on published and presented literature. They are provided to support your independent review and are not intended to be submitted verbatim as your own clinical analysis. Before incorporating any of the following content into a letter of medical necessity, you must review each data point, assess its applicability to your patient's specific clinical circumstances, and restate the relevant information in your own words reflecting your independent medical judgment.]

- **[Survival Benefit**
  - In the integrated survival analysis in the Lembaz Prescribing Information, Lembaz reduced the risk of death by 55% compared with matched external controls (HR: 0.45; 95% CI: 0.21, 0.95). Median survival was 102 months versus 59 months, with deaths in 12 of 36 Lembaz-treated patients (33.3%) versus 24 of 36 matched controls (66.9%)[7]
  - In a primary analysis comparing patients with I-NPC treated with intrathecal Lembaz across clinical studies and EAP (n=72) with matched external controls receiving usual care obtained from four major disease databases or publications (n=119), Lembaz demonstrated a 71% reduction in the risk of death (HR: 0.289; 95% CI: 0.141, 0.593), with a 5-year survival rate of 84% in treated patients vs 42% in matched controls[8]
    - The integrated survival analysis in the Lembaz Prescribing Information and the supportive analysis results differ because they come from two separate analyses of different patient groups, so the figures are not directly comparable
  - These outcomes are further supported by objective biomarker evidence: CSF levels of 24(S)-hydroxycholesterol, a validated marker of neuronal cholesterol trafficking, increased, while CSF calbindin D and FABP3, established markers of neuronal injury, decreased, providing mechanistic evidence that Lembaz directly addresses the underlying disease pathophysiology[9]
    - The clinical significance of these biomarker changes has not been established
  - No previously approved NPC therapy is indicated for improved survival.[2,4,10-12] Based on the level of urgency associated with NPC and the strength of the clinical evidence, I respectfully request that this prior authorization be processed on an expedited basis and without delay]
- [**Importance of Early Intervention**
  - Patients with NPC face markedly reduced survival, with earlier age of symptom onset predicting earlier mortality.[3] For early I-NPC and late I-NPC, defined as ages of neurological symptom onset as <2 years and 2 to <6 years, respectively (and not the patient's current age), the estimated mean age of death is 5.6 years and 13.4 years.[5,13] These subtypes have the poorest prognosis in NPC, with rapid progression to neurologic symptoms and decline[1,3,5,13]
  - Clinical data show a significant reduction in the risk of death with Lembaz vs untreated matched controls in these poorly prognostic subgroups: an 85% reduction in risk of death for early I-NPC (HR: 0.148; 95% CI: 0.064, 0.343; $p$<0.0001) and a 66% reduction in risk of death for late-infantile-onset NPC (HR: 0.344; 95% CI: 0.146, 0.812; $p$=0.0457)[9]
  - These data underscore why early intervention with Lembaz before irreversible neurodegeneration is critical to supporting improved survival for patients with infantile-onset NPC]
- [**Concomitant Therapy**

- The progressive, degenerative nature of NPC has clinicians to evaluate various treatment approaches, with the 2025 Consensus Clinical Management Guidelines for NPC recommending consideration of monotherapy and combination therapeutic strategies[14]
- Investigators have found that Lembaz monotherapy and Lembaz in combination with miglustat significantly improve survival in patients with infantile-onset NPC, achieving 86% (HR: 0.139; 95% CI: 0.049, 0.398; $p<0.0001$) and 64% reduction in death, respectively (HR: 0.361; 95% CI: 0.173, 0.752; $p=0.0205$)[8]
- Investigators have found that a treatment paradigm in which Lembaz serves as foundational therapy and complementary agents may be layered to address additional aspects of disease biology in I-NPC[15]
- In an analysis of Lembaz alone or in combination with arimoclomol or with levacetylleucine, investigators found that combination treatment resulted in comparable targeting of the central pathogenic biology of NPC (eg, synaptic network growth, oligodendrocyte maturation, myelination), and at lower concentrations than monotherapy in an *in vitro* mouse model[16]
    - These findings are derived entirely from *in vitro* mouse (*NPC1*$^{-}$/$^{-}$) primary culture models; translational relevance to human disease has not been established[17]]

**REFERENCES:**

**1.** Burton BK et al. Estimating the prevalence of Niemann-Pick disease type C (NPC) in the United States. *Mol Genet Metab*. 2021;134(1-2):182-187. doi:10.1016/j.ymgme.2021.06.011 **2.** Berry-Kravis E. Niemann-Pick disease, type C: diagnosis, management and disease-targeted therapies in development. *Semin Pediatr Neurol.* 2021;37:100879. **3.** Bianconi SE et al. Evaluation of age of death in Niemann-Pick disease, type C: utility of disease support group websites to understand natural history. *Mol Genet Metab.* 2019;126(4):466-469. doi:10.1016/j.ymgme.2019.02.004 **4.** Vanier MT. Niemann-Pick disease type C. *Orphanet J Rare Dis*. 2010; 5:16. doi:10.1186/1750-1172-5-1 **5.** Imrie J, Heptinstall L, Knight S, Strong K. Observational cohort study of the natural history of Niemann-Pick disease type C in the UK: a 5-year update from the UK clinical database. *BMC Neurol*. 2015;15:257. doi:10.1186/s12883-015-0511-1 **6**. Kassen S, Parseghian C, Andrews P, et al. Niemann-Pick type c patient and caregiver voices: externally-led, patient-focused drug development meeting. Niemann-Pick Type C Patient-Focused Drug Development. September 2019. Accessed June 10, 2026. https://niemannpickc-pfdd.com/wp-content/uploads/2020/05/NPC-PFDD-Voice-of-the-Patient-report-ver2-1.pdf **7.** Lembaz Prescribing Information. Beren Therapeutics P.B.C. **8.** Berry-Kravis E, Keller LH, Jiao L, et al. Substantial survival benefit and slowing of disease progression with adrabetadex treatment in individuals with infantile-onset Niemann-Pick disease type C (NPC). Poster presented at: WORLDSymposium; February 3-6, 2026; San Diego, CA. Poster LB-13 **9.** Porter FD et al. Efficacy of intrathecal adrabetadex in infantile-onset Niemann-Pick Disease type C is supported by survival, clinical, and biomarker data. Poster presented at: 46th Annual Meeting of the Society for Inherited Metabolic Disorders (SIMD); May 17-20, 2026. **10.** Miplyffa. Prescribing Information. Zevra Therapeutics Inc; 2025. **11.** Aqneursa. Prescribing Information. IntraBio. 2024**. 12.** Zavesca. Prescribing Information. Actelion Pharmaceuticals US, Inc. 2022. **13.** Bolton SC, Soran V, Marfa MP, et al. Clinical disease characteristics of patients with Niemann-Pick disease type C: findings from the International Niemann-Pick Disease Registry (INPDR). *Orphanet J Rare Dis*. 2022;17(1):51. doi:10.1186/s13023-022-02200-4 **14.** Hiwot T, Porter FD, Bremova-Ertl T, et al. 2025 consensus clinical management guidelines for Niemann-Pick disease type C. *J Inherit Metab Dis.* 2026;49(3):e70185. doi:10.1002/jimd.70185 **15.** Burchard J, Richard P, Jo S, et al. Adrabetadex alone or in combination with arimoclomol and levacetylleucine promotes oligodendrocyte proliferation, synaptic network growth, and myelination in an in vitro mouse model of Niemann-Pick disease type C. Poster presented at: 2026 Ara Parseghian Medical Research Fund Conference; May 30-June 2, 2026; Tucson, AZ. **16.** Berry-Kravis E, Keller LH, Jiao L, et al. Early evidence of an emerging NPC treatment paradigm: adrabetadex use alongside arimoclomol and/or N-acetyl-L-leucine. Poster presented at: 2026 Ara Parseghian

Medical Research Fund Conference; May 30-June 2, 2026; Tucson, AZ. Poster 6. **17.** Data on file. Beren Therapeutics P.B.C.

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