HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LEMBAZ safely and effectively. See full prescribing information for LEMBAZ.

LEMBAZ™ (adrabetadex) injection, for intrathecal use
Initial U.S. Approval: 2026

WARNING: HEARING IMPAIRMENT INCLUDING PERMANENT HEARING LOSS
See full prescribing information for complete boxed warning.

- **Treatment with LEMBAZ has resulted in permanent hearing impairment. (5.1)**
- **Prior to LEMBAZ use, perform a comprehensive audiology evaluation (*e.g.*, pure tone audiometry, speech recognition, tympanometry) to establish baseline hearing levels. (5.1)**
- **During LEMBAZ treatment, modify the LEMBAZ dosage based on results of comprehensive audiology evaluations as recommended. (2.3)**

----------INDICATIONS AND USAGE----------
LEMBAZ 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. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Prior to LEMBAZ treatment, perform a comprehensive audiology evaluation to establish baseline hearing levels. (2.1, 5.1)
- Administer LEMBAZ intrathecally over 1 to 2 minutes. (2.2)
- Recommended starting LEMBAZ dosage in patients who weigh 7 kg or greater is the following (2.2):
  - Less than 6 months of age is 100 mg every two weeks.
  - 6 months of age to less than 4 years of age is 200 mg every two weeks.
  - 4 years of age or older is 400 mg every two weeks.
- Refer to the Full Prescribing Information for detailed instructions on (2.3, 2.4):
  - Maximum recommended LEMBAZ dosage;
  - Recommended frequency of comprehensive audiology evaluations during LEMBAZ treatment;
  - Upward titration and dosage modification for hearing impairment, ataxia, and fatigue.
- Refer to the Full Prescribing Information for detailed preparation and administration instructions and storage of diluted LEMBAZ solution. (2.6, 2.7, 2.8)

---------- DOSAGE FORMS AND STRENGTHS ----------
Injection: 900 mg/4.5 mL (200 mg/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
None. (4)

---------- WARNINGS AND PRECAUTIONS----------
- *Hearing Impairment Including Permanent Hearing Loss*: See Full Prescribing Information for recommendations on comprehensive audiology evaluations prior to and during LEMBAZ treatment, and other recommendations to mitigate the ototoxicity risk. (5.1)
- *Ataxia*: Consider reducing the LEMBAZ dosage to reduce ataxia severity. (5.2)
- *Fatigue*: Consider reducing the LEMBAZ dosage to reduce fatigue severity. (5.3)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (reported in ≥25% of patients) included hearing impairment, ataxia, fatigue, vomiting, back pain, headache, pyrexia, diarrhea, nausea, and cough. (6.1)

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.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: HEARING IMPAIRMENT INCLUDING PERMANENT HEARING LOSS

Treatment with LEMBAZ has resulted in permanent hearing impairment. Recommendations to mitigate the ototoxicity risk are as follows:

- **Prior to LEMBAZ use, perform a comprehensive audiology evaluation (*e.g.*, pure tone audiometry, speech recognition, tympanometry) to establish baseline hearing levels *[see Warnings and Precautions (5.1)]*.**
- **During LEMBAZ treatment, modify the LEMBAZ dosage based on comprehensive audiology evaluations as follows *[see Dosage and Administration (2.3)]*:**
  - **To determine the subsequent dosage level, repeat the 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 evaluation every 12 months.**

1 INDICATIONS AND USAGE

LEMBAZ™ 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Recommendations Prior to Initiation of LEMBAZ Treatment

Prior to initiation of LEMBAZ treatment, perform a baseline comprehensive audiology evaluation (*e.g.*, pure tone audiometry, speech recognition, tympanometry) to establish baseline hearing levels *[see Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage and Administration

Administer LEMBAZ intrathecally over 1 to 2 minutes by, or under the supervision of, a healthcare provider experienced in performing lumbar punctures *[see Dosage and Administration (2.4)]*. See Table 1 for the recommended starting dosage and the recommended maximum dosage for LEMBAZ in patients who weigh 7 kg or greater. After at least 2 doses at each dosage level (a *dosage level* consists of the same dose of LEMBAZ given two weeks apart), titrate the LEMBAZ dosage upward in 100-mg to 200-mg increments as tolerated, up to the maximum recommended dosage.

See dosage modifications due to hearing loss *[see Dosage and Administration (2.3)]* and dosage modifications due to ataxia and fatigue *[see Dosage and Administration (2.4)]*.

Table 1: Recommended Starting and Maximum Dosage for LEMBAZ

Patient Age	Recommended Starting Dosage*	Recommended Maximum Dosage (by Patient Weight)
Less than 6 months	100 mg every two weeks	If 7 kg to less than 12 kg, maximum dosage is 600 mg every two weeks.
6 months to less than 4 years	200 mg every two weeks	• If 7 kg to less than 12 kg, maximum dosage is 600 mg every two weeks. • If 12 kg or more, maximum dosage is 900 mg every two weeks.
4 years and older	400 mg every two weeks	• If 7 kg to less than 12 kg, maximum dosage is 600 mg every two weeks. • If 12 kg or more, maximum dosage is 900 mg every two weeks.

*After at least 2 doses at each dosage level, titrate the LEMBAZ dosage upward in 100-mg to 200-mg increments as tolerated, up to the maximum recommended dosage.

2.3 Dosage Modifications for Hearing Loss

During LEMBAZ treatment to determine the subsequent dosage level, repeat the 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 (see Table 2).

Table 2: LEMBAZ Dosage Titration Recommendations Based on Audiology Results

Baseline Hearing Status	Audiology Testing Results (Hearing Monitoring Results)	Recommendation
No Baseline Hearing Impairment	• No hearing impairment observed at frequencies below 4,000 Hz, OR • Hearing impairment observed but with a hearing threshold less than or equal to 40 dB HL at frequencies below 4,000 Hz	May increase the dosage.
	Hearing impairment with a threshold greater than 40 dB HL at frequencies below 4,000 Hz (hearing impairment in the speech hearing range)	Do not increase the dosage.
Baseline Mild to Moderate Hearing Impairment	• No hearing threshold shift at 2 consecutive frequencies below 4,000 Hz, OR • Hearing threshold shift that is not greater than 15 dB at 2 consecutive frequencies below 4,000 Hz	May increase the dosage.
	Hearing threshold shift of greater than 15 dB at 2 consecutive frequencies below 4,000 Hz	Do not increase the dosage.

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 evaluation every 12 months.

In patients with LEMBAZ-associated hearing impairment, there are insufficient data to determine if continuing LEMBAZ treatment at the current dosage level increases the risk of further hearing impairment or if lowering the LEMBAZ dosage reduces the risk of further hearing impairment *[see Warnings and Precautions (5.1)]*.

2.4 Dosage and Administration Modifications Due to Ataxia or Fatigue

In patients with severe ataxia or fatigue associated with LEMBAZ treatment, consider reducing the LEMBAZ dosage *[see Warnings and Precautions (5.2, 5.3)]*. If the LEMBAZ dosage is decreased due to severe ataxia or fatigue and the ataxia or fatigue becomes mild or resolves, then consider increasing the LEMBAZ dosage. Subsequently, if the ataxia or fatigue worsens in severity, then consider decreasing LEMBAZ dosing.

2.5 Recommendations Regarding a Missed Dose(s)

If one or more LEMBAZ doses are missed, restart LEMBAZ treatment as soon as possible, maintaining the 2-week interval between intrathecal administrations thereafter. Do not administer an extra LEMBAZ dose to compensate for a missed dose.

2.6 Preparation Instructions

Prepare LEMBAZ for intrathecal injection according to the following steps using aseptic technique:

1. Visually inspect the solution in the vials for particulate matter and discoloration. The solution should be clear and colorless. Discard LEMBAZ if the solution is discolored or if visible particulate matter is present.
2. Withdraw the required volume of LEMBAZ from the vial and discard unused contents of the vial.
3. Dilute LEMBAZ with 0.9% Sodium Chloride Injection (preservative free) to a total administration volume of 3 mL, 5 mL, or 10 mL based on patient's weight (see Tables 3, 4, and 5, respectively). For patients who

weigh 7 kg to less than 12 kg treated with LEMBAZ 600-mg dose, do not dilute LEMBAZ (a volume of 3 mL is administered undiluted in these patients).

4. Attach a syringe cap to the syringe if not administered immediately.

Table 3: Administration Volumes of LEMBAZ and the Diluent by Patient Weight for Patients Who Weigh 7 kg to Less than 12 kg

LEMBAZ Dose	Volume of LEMBAZ	Volume of 0.9% Sodium Chloride Injection	Total Volume for Intrathecal Administration
100 mg	0.5 mL	2.5 mL	3 mL
200 mg	1 mL	2 mL	3 mL
300 mg	1.5 mL	1.5 mL	3 mL
400 mg	2 mL	1 mL	3 mL
500 mg	2.5 mL	0.5 mL	3 mL
600 mg*,†	3 mL	0 mL	3 mL

*Maximum dose for weight.
†For patients who weigh 7 kg to less than 12 kg on the LEMBAZ 600-mg dose, the LEMBAZ dose volume of 3 mL is administered undiluted.

Table 4: Administration Volumes of LEMBAZ and the Diluent by Patient Weight for Patients Who Weigh 12 kg to 25 kg

LEMBAZ Dose	Volume of LEMBAZ	Volume of 0.9% Sodium Chloride Injection	Total Volume for Intrathecal Administration
200 mg	1 mL	4 mL	5 mL
300 mg	1.5 mL	3.5 mL	5 mL
400 mg	2 mL	3 mL	5 mL
500 mg	2.5 mL	2.5 mL	5 mL
600 mg	3 mL	2 mL	5 mL
750 mg	3.75 mL	1.25 mL	5 mL
900 mg*	4.5 mL	0.5 mL	5 mL

*Maximum dose for weight.

Table 5: Administration Volumes of LEMBAZ and the Diluent by Patient Weight for Patients Who Weigh Greater than 25 kg

LEMBAZ Dose	Volume of LEMBAZ	Volume of 0.9% Sodium Chloride Injection	Total Volume for Intrathecal Administration
200 mg	1 mL	9 mL	10 mL
300 mg	1.5 mL	8.5 mL	10 mL
400 mg	2 mL	8 mL	10 mL
500 mg	2.5 mL	7.5 mL	10 mL
600 mg	3 mL	7 mL	10 mL
750 mg	3.75 mL	6.25 mL	10 mL
900 mg*	4.5 mL	5.5 mL	10 mL

*Maximum dose for weight.

2.7 Storage of the Diluted LEMBAZ Solution

If the diluted LEMBAZ solution is not administered immediately, store it at room temperature at 20°C to 25°C (68°F to 77°F). Note that when administering the LEMBAZ 600-mg dose to patients who weigh 7 kg to less than 12 kg, administer LEMBAZ undiluted. Administer LEMBAZ within 8 hours or discard.

2.8 Administration Instructions

Consider the following concomitant therapy prior to intrathecal administration of LEMBAZ:

- Apply local anesthetic (topical and subcutaneous lidocaine) to the intended injection site.

- Consider sedation as indicated by the clinical condition of the patient.

Recommended LEMBAZ administration instructions, under aseptic conditions, are as follows:

1. If there is difficulty accessing the intrathecal space, consider imaging to guide intrathecal administration of LEMBAZ.
2. Prior to LEMBAZ administration, remove up to 5 mL of cerebrospinal fluid (CSF).
3. Administer LEMBAZ as an intrathecal bolus injection over 1 to 2 minutes using a spinal needle. Do not administer LEMBAZ in areas of the skin where there are signs of infection or inflammation.
4. After administration, keep patients in the Trendelenburg position (head down at 15 to 30 degrees) for approximately 40 minutes. If unable to tolerate the Trendelenburg position, keep the patient flat as tolerated for about 40 minutes.

3 DOSAGE FORMS AND STRENGTHS

Injection: 900 mg/4.5 mL (200 mg/mL) of adrabetadex as a sterile, clear, colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hearing Impairment Including Permanent Hearing Loss

LEMBAZ can cause hearing impairment. LEMBAZ-treated patients experienced permanent hearing impairment that ranged from mild to profound hearing loss, including in some patients with normal hearing at baseline. Observed hearing impairment predominantly impacted higher frequencies (at least 2,000 to 8,000 Hz) but hearing impairment at mid and lower frequencies (500 to 2,000 Hz) was also observed *[see Adverse Reactions (6.1)]*.

Recommendations to mitigate the ototoxicity risk are as follows:

- Prior to LEMBAZ use, perform a comprehensive audiology evaluation (*e.g.*, pure tone audiometry, speech recognition, tympanometry) to establish baseline hearing levels *[see Dosage and Administration (2.1)]*.
- During LEMBAZ treatment, modify the LEMBAZ dosage based on comprehensive audiology evaluations as follows:
    - To determine the subsequent dosage level (a *dosage level* consists of the same dose of LEMBAZ given two weeks apart), repeat the 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 evaluation every 12 months.
- Do not increase the dosage if hearing impairment is observed as defined in subsection 2.3 *[see Dosage and Administration (2.3)]*.

In patients with LEMBAZ-associated hearing impairment, there are insufficient data to determine if continuing treatment at the current dosage increases the risk of further hearing impairment or if lowering the LEMBAZ dosage reduces the risk of additional hearing impairment.

5.2 Ataxia

LEMBAZ can cause ataxia, including fall, abnormal gait and/or coordination, dizziness, and hypotonia. In a clinical trial in patients with NPC (Trial 1) *[see Clinical Studies (14)]*, of the patients who received LEMBAZ dosage of 900 mg or less every 2 weeks and who experienced ataxia, most developed ataxia within 3 days of LEMBAZ administration *[see Adverse Reactions (6.1)]*. One patient treated with LEMBAZ 900 mg every

2 weeks experienced severe ataxia requiring hospitalization. The severity of ataxia may be associated with a higher LEMBAZ dosage.

Monitor LEMBAZ-treated patients for ataxia severity. In patients with severe ataxia associated with LEMBAZ treatment, consider reducing the LEMBAZ dosage to reduce ataxia severity *[see Dosage and Administration (2.4)]*.

5.3 Fatigue

LEMBAZ can cause fatigue, including asthenia, fatigue, malaise, and somnolence. In a clinical trial in patients with NPC (Trial 1) *[see Clinical Studies (14)]*, of the patients who received LEMBAZ dosage of 900 mg or less every 2 weeks and who experienced fatigue, most developed fatigue within 3 days of LEMBAZ administration *[see Adverse Reactions (6.1)]*. One patient treated with LEMBAZ 900 mg every 2 weeks required hospitalization for a severe fatigue event on the day of treatment. The severity of fatigue may be associated with a higher LEMBAZ dosage.

Monitor LEMBAZ-treated patients for fatigue. In patients with severe fatigue associated with LEMBAZ treatment, consider reducing the LEMBAZ dosage to reduce fatigue severity *[see Dosage and Administration (2.4)]*.

6 ADVERSE REATIONS

The following adverse reactions are described below and elsewhere in the labeling:

- Hearing Impairment Including Permanent Hearing Loss *[see Warnings and Precautions (5.1)]*
- Ataxia *[see Warnings and Precautions (5.2)]*
- Fatigue *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of LEMBAZ was evaluated in 141 patients with NPC (including 80 patients with NPC with neurological symptom manifestation onset at less than 6 years of age) who received at least one LEMBAZ dose given by intrathecal administration *[see Clinical Studies (14)]*. The safety and effectiveness of LEMBAZ for the treatment of NPC in patients with neurological manifestations that started at 6 years of age or older has not been established *[see Indications and Usage (1)].*

Trial 1 Part A/B was a 52-week, double-blind, sham-control trial in 56 patients with NPC who received intrathecal LEMBAZ every 2 weeks for 52 weeks or sham treatment *[see Clinical Studies (14)]*. LEMBAZ-treated patients in Trial 1 in:

- Part A received a dosage of 900 mg every 2 weeks, 1,200 every 2 weeks (1.3 times the maximum recommended dosage), or 1,800 mg every 2 weeks (twice the maximum recommended dosage).
- Part B received a dosage of 900 mg every 2 weeks.

Six patients received at least one dose above 900 mg *[see Overdosage (10)]*.

There were 32 patients who received up to 900 mg in the LEMBAZ treatment group and 18 in the sham-control group with a mean age of 12 years old (minimum age 4, maximum age 22). Patients in Trial 1 were 24 female (48%), 26 male (52%). Race was reported as 41 White (82%), 5 Asian (10%), Black or African American 1 (2%), Multiple 1 (2%), or Other 2 (4%). Ethnicity was reported as 6 (12%) Hispanic or Latino and 41 (82%) as Not Hispanic or Latino. Twenty-eight patients (56%) experienced neurological symptom onset at <6 years of age.

The most common adverse reactions (≥25% of patients treated with LEMBAZ and greater in LEMBAZ-treated patients than those in the sham control group) were hearing impairment, ataxia, fatigue, vomiting, back pain, headache, pyrexia, diarrhea, nausea, and cough. Table 6 summarizes the common adverse reactions (reported

in ≥10% of LEMBAZ-treated patients, and greater in LEMBAZ-treated patients than those in the sham control group) that occurred in the 32 LEMBAZ-treated patients receiving up to 900 mg in Trial 1.

Table 6: Common Adverse Reactions* in Patients with NPC through Week 52 in Trial 1 Parts A and B

Preferred Term	LEMBAZ† N=32 n (%)	Sham N=18 n (%)
Hearing impairment‡	23 (71.9)	8 (44.4)
Ataxia§	22 (68.8)	5 (27.8)
Fatigue¶	18 (56.3)	5 (27.8)
Vomiting#	17 (53.1)	3 (16.7)
Back pain	16 (50.0)	3 (16.7)
Headacheᵇ	14 (43.8)	3 (16.7)
Pyrexia	13 (40.6)	3 (16.7)
Diarrhea	10 (31.3)	1 (5.6)
Nausea	8 (25.0)	1 (5.6)
Cough	8 (25.0)	4 (22.2)
Contusion	6 (18.8)	2 (11.1)
Pain in extremity	6 (18.8)	1 (5.6)
Epistaxis	5 (15.6)	1 (5.6)
Urinary incontinence	5 (15.6)	1 (5.6)
Muscular weakness	5 (15.6)	0 (0)
Dysarthria	4 (12.5)	1 (5.6)
Skin abrasion	4 (12.5)	1 (5.6)
Nasopharyngitis	4 (12.5)	2 (11.1)

*Common adverse reactions were those reported in ≥10% of LEMBAZ-treated patients, and greater in LEMBAZ-treated patients than those in the sham control group.
†Subgroup of treatment arm that received LEMBAZ ≤900 mg.
‡Hearing impairment includes other similar terms and hypoacusis, tinnitus, deafness, and abnormal tympanometry.
§Ataxia includes gait disturbance, fall, dizziness, dyskinesia, balance disorder, bradykinesia, abnormal coordination, dysstasia, vertigo.
¶Fatigue includes asthenia, malaise, somnolence.
#Vomiting includes procedural vomiting.
ᵇHeadache includes procedural headache.

Adverse Reactions in Patients Less than 4 years of Age

In Trial 3 and an expanded access program, 23 patients less than 4 years of age received a starting LEMBAZ dosage of 200 mg every 2 weeks given intrathecally, and the dosage was increased up to a maximum of 600 mg (for patients who weighed 7 to 12 kg) or 900 mg (for patients who weighed more than 12 kg) every 2 weeks given intrathecally. Adverse reactions were similar when compared to patients 4 years of age or older who received LEMBAZ at a dosage up to 900 mg in Trial 1.

Description of Selected Adverse Reactions of Interest

Hearing Impairment: In single-arm studies (Trial 3 and an expanded access program) *[see Clinical Studies (14)]*, the safety of LEMBAZ was assessed in 59 patients who received a starting LEMBAZ dosage of 200 mg every 2 weeks given intrathecally (less than 4 years of age), or 400 mg every 2 weeks (4 years of age or older) given intrathecally. The dosage was increased to a maximum of up to 600 mg (for patients who weighed 7 to 12 kg) or up to 900 mg (for patients who weighed more than 12 kg) given intrathecally every 2 weeks. In Trial 3 and an expanded access program which used upward titration guided by audiometry, 37% (22/59) of patients treated with LEMBAZ experienced hearing impairment *[see Warnings and Precautions (5.1)]*.

Ataxia: Of the ataxia adverse reactions that occurred in LEMBAZ-treated patients, the ataxia started within 3 days of LEMBAZ administration in 61% (107/174) of events. The duration of ataxia ranged from 1 to

476 days, with a median duration of 2 days. Ataxia adverse reactions resulted in dosage interruptions in 6% (2/32) of LEMBAZ-treated patients *[see Warnings and Precautions (5.2)]*.

Fatigue: Of the fatigue adverse reactions that occurred in LEMBAZ-treated patients, the fatigue started within 3 days of LEMBAZ administration in 91% (87/96) of events. The duration of fatigue ranged from 1 to 76 days, with a median duration of 2 days *[see Warnings and Precautions (5.3)]*.

Aspiration Pneumonia: In Trial 1 Parts A and B, 9% (3/32) of LEMBAZ-treated patients experienced aspiration pneumonia compared to 6% (1/18) of sham-treated patients. In Trial 1 Part C, a single patient experienced an aspiration event resulting in fatal aspiration pneumonia after they received LEMBAZ with sedation. It is unclear whether the aspiration pneumonia was due to LEMBAZ, sedation, and/or underlying NPC disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on the use of LEMBAZ in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

In animal reproduction studies, intravenous administration of adrabetadex to pregnant rats or rabbits during organogenesis at dose exposures that are 2 and 4 times greater than the maximum recommended human dose (MRHD) based on body surface area resulted in no adverse developmental effects (*see Data*).

The background risk of major birth defects and miscarriage for females with NPC with neurological manifestations is unknown. All pregnancies have a background risk of birth defects, loss, and other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: Embryofetal development studies were conducted in pregnant rats and rabbits administered intravenous adrabetadex once daily during organogenesis at doses up to 400 mg/kg/day (2 and 4 times greater than the MRHD based on body surface area). No adverse developmental effects were observed at any dose.

In a pre-postnatal development study conducted in pregnant rats administered intravenous adrabetadex once daily from Gestation Day (GD) 16 through lactation at doses up to 400 mg/kg/day, there was no maternal toxicity; however, pup survival was decreased at 400 mg/kg/day (2 times the MRHD based on body surface area).

In a second pre-postnatal development study in pregnant rats administered intravenous adrabetadex once daily at doses up to 400 mg/kg/day, there were no adverse effects observed in either the F1 or F2 generations at doses up to 400 mg/kg/day (2 times the MRHD based on body surface area).

8.2 Lactation

Risk Summary

There are no data on the presence of adrabetadex in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LEMBAZ and any potential adverse effects on the breastfed infant from LEMBAZ or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of LEMBAZ have been established to reduce the risk of mortality in pediatric patients, who weigh 7 kg or greater, with NPC with neurological manifestations that started at less than 6 years of age. Use of LEMBAZ for this indication is supported by evidence from integrated analyses of 1 randomized, controlled trial, 2 open-label, single-arm clinical trials, and an expanded access program compared to data from an untreated, contemporaneous, external cohort *[see Warnings and Precautions (5), Adverse Reactions (6.1), and Clinical Studies (14)]*.

The safety and effectiveness of LEMBAZ have not been established to reduce the risk of mortality in pediatric patients with NPC who weigh less than 7 kg or in pediatric patients who developed neurological manifestations starting at 6 years of age and older.

Juvenile Animal Toxicity Data

In a cat model of NPC, juvenile cats were administered adrabetadex intrathecally at doses of 30, 60, or 120 mg every 14 days, beginning at 3 weeks of age (equivalent to a 6-month-old human infant) and continuing through approximately 24 weeks of age. The highest-dose group also received an additional subcutaneous dose of adrabetadex at 1,000 mg/kg weekly. Progressive hearing loss was observed in all treatment groups beginning at 8 weeks of age and increasing in a dose-dependent manner with repeated dosing. Hearing loss was irreversible following treatment cessation, with no improvement in hearing threshold observed up to 12 weeks after the last dose *[see Warnings and Precautions (5.1)]*.

Juvenile rats were administered 50, 200, or 400 mg/kg/day of adrabetadex intravenously once daily from postnatal day (PND) 16 through 44 (plasma exposures 0.6, 3.2, and 4.7 times the MRHD based on AUC at PND 16). Dose-related increases in kidney weights that correlated with slight to moderate diffuse microvacuolation of the cortical tubules were observed at 200 mg/kg/day or more. A dose of 50 mg/kg/day was the NOAEL. Hearing was not assessed in this study.

8.5 Geriatric Use

Clinical studies of LEMBAZ did not include patients 65 years of age and older to determine if they respond differently from younger adult patients.

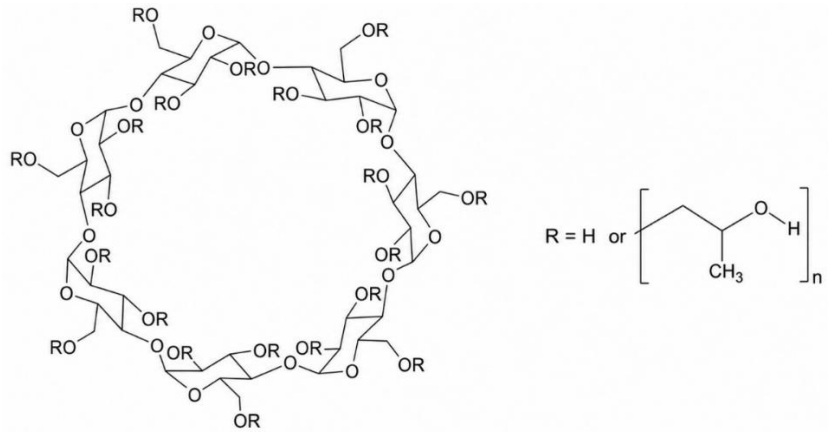
10 OVERDOSAGE

In Trial 1 Part A *[see Clinical Studies (14)]*, 3 patients received 1,200 mg of LEMBAZ (1.3 times maximum recommended dosage) and 3 patients received 1,800 mg of LEMBAZ (2 times the maximum recommended dosage). There was a higher rate of ataxia and fatigue, and greater severity of hearing impairment, ataxia, and fatigue in patients who received these dosages, compared to those who received the maximum recommended dose of 900 mg.

If an overdose of LEMBAZ occurs, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for overdose management recommendations.

11 DESCRIPTION

Adrabetadex is a mixture of 2-hydroxypropyl-substituted beta cyclodextrin(s). The empirical formula is $(C_6H_{10}O_5)_7(C_3H_6O)_n$, where n=4.1 to 4.8, and the average molecular weight is approximately 1,371 to 1,432 g/mol. The chemical structure is:



LEMBAZ (adrabetadex) injection is a sterile, preservative-free, clear, colorless solution in a single-dose vial for intrathecal use. Each 1 mL contains 200 mg of adrabetadex and inactive ingredients sodium chloride USP (2 mg) and Water for Injection USP. The pH is adjusted with hydrochloric acid and sodium hydroxide as needed. The pH is 6.0 to 8.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism(s) by which LEMBAZ exerts its clinical effects to reduce the risk of mortality in adult and pediatric patients who weigh 7 kg or greater with NPC with neurological manifestations that started at less than 6 years old has not been fully characterized. Adrabetadex has binding affinity for cholesterol and reduces lipid and ganglioside accumulation in the context of NPC by trafficking cholesterol out of the lysosome.

12.2 Pharmacodynamics

Following 52 weeks of treatment with LEMBAZ in patients with NPC, increased concentration of 24(S)-hydroxycholesterol and decreased concentrations of calbindin D and FABP3 in CSF were observed compared to baseline. The clinical significance of these biomarker changes has not been established. Plasma 24(S)-hydroxycholesterol and CSF calbindin D and FABP3 changed in an exposure-dependent manner across the LEMBAZ dosage range of 200 to 900 mg administered intrathecally every 2 weeks.

The exposure-response relationship and the time course of the safety and effectiveness of LEMBAZ has not been fully characterized.

12.3 Pharmacokinetics

The pharmacokinetic parameters of adrabetadex in the plasma following intrathecal administration of LEMBAZ in patients with NPC are summarized in Table 7. Plasma $AUC_{0\text{-last}}$ increased in an approximately dose proportional manner and plasma C_{max} increased less than dose proportionally at a dose that ranged from 200 to 900 mg. No adrabetadex accumulation in plasma or CSF was observed after repeated LEMBAZ administration.

Table 7: Mean (CV%) Pharmacokinetic Parameters of Adrabetadex in Plasma Following Intrathecal Administration of LEMBAZ in Patients with NPC

	Intrathecal Dose of LEMBAZ			
	200 mg	**300 mg**	**600 mg**	**900 mg**
$AUC_{0\text{-last}}$ (hr·mcg/mL)	39 (19%)	51 (14%)	101 (34%)	167 (40%)
C_{max} (mcg/mL)	2.4 (33.7%)	4.5 (77.3%)	6.3 (37%)	8.4 (84.3%)

Absorption

Following intrathecal injection of LEMBAZ, the median time to peak plasma concentration (T_{max}) of adrabetadex ranged from 4 to 8 hours. The absolute bioavailability of adrabetadex following intrathecal administration of LEMBAZ has not been determined.

Distribution

Following intrathecal administration of LEMBAZ, the mean apparent volume of distribution of adrabetadex at steady state was 61.8 L in patients with NPC. Plasma protein binding of adrabetadex is less than 10% over the concentration range from 1 to 10 micromole.

Elimination

The mean plasma half-life of adrabetadex was 14.7 hours, following intrathecal LEMBAZ administration.

Metabolism: The metabolism of adrabetadex has not been characterized.

Excretion: Adrabetadex is expected to be predominantly cleared by urinary excretion.

Specific Populations

Patients with Renal or Hepatic Impairment: No clinical studies have been conducted to evaluate the pharmacokinetics of adrabetadex in patients with renal or hepatic impairment. Systemic exposure of adrabetadex is expected to be higher in patients with renal impairment, which is not considered clinically significant.

Drug Interaction Studies

In vitro Studies

- *CYP Enzymes*: Adrabetadex is not a substrate or inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4, or an inducer of CYP1A2, 2B6, or 3A4.
- *Transporter Systems*: Adrabetadex is not a substrate of organic anion transporter (OAT)1 and OAT3, organic cation transporter (OCT)2, multidrug and toxin extrusion protein (MATE)1, MATE2-K, OATP1B1, OATP1B3, BCRP, or P-glycoprotein (P-gp). Adrabetadex is not an inhibitor of bile salt export pump (BSEP), OAT1, OAT3, OCT2, MATE1, MATE2-K, OATP1B3, or P-gP transporters. Adrabetadex inhibits OATP1B1 and BCRP transporters, but the clinical significance is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies of adrabetadex were conducted in mice and rats with oral administration by dietary admixture. There was no evidence of a primary carcinogenic effect in mice given daily oral doses of up to 5,000 mg/kg for approximately 2 years. In rats, administration of adrabetadex at 5,000 mg/kg/day (11 times greater than the MRHD based on body surface area) for approximately 2 years increased the incidence of soft tissue combined malignant sarcoma and fibrosarcoma in males and exocrine pancreatic tumors (benign adenoma and combined benign adenoma/malignant adenocarcinoma) in females.

Mutagenesis

Adrabetadex was not mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), unscheduled DNA synthesis in primary rat hepatocytes, mouse lymphoma forward mutation, chromosomal aberration in human lymphocytes, and mouse micronucleus assays.

Impairment of Fertility

In a fertility and early embryonic development study, intravenous administration of adrabetadex to rats once daily from 14 days prior to mating for females and 60 days prior to mating for males, and continuing through GD 8 at doses up to 400 mg/kg/day (2 times the MRHD based on body surface area) did not adversely affect fertility.

14 CLINICAL STUDIES

The effectiveness of LEMBAZ to reduce the risk of mortality in adult and pediatric patients, who weigh 7 kg or greater, with NPC with neurological manifestations onset prior to 6 years of age was established based on an integrated survival analysis of data from Trials 1, 2, 3, an expanded access program, and Study 1. The integrated survival analysis using these data sources included only patients with neurological manifestations onset prior to 6 years old (the safety and effectiveness of LEMBAZ to reduce mortality in patients with NPC with neurological manifestation onset at 6 years of age or older has not been established *[see Indications and Usage (1)]*).

- Trial 1 was a trial in patients aged 4 to 21 years old and with onset of neurological manifestations prior to 15 years old, and included Parts A, B, and C:
  - Part A and Part B (NCT02534844) included a 52-week, randomized, double-blind, and sham-controlled period and enrolled 56 treatment-naïve patients. In Part A, the LEMBAZ intrathecal dosage was 900 mg every two weeks, 1,200 mg every two weeks (1.3 times the maximum recommended dosage), and 1,800 mg every two weeks (twice the maximum recommended dosage) and in Part B, the LEMBAZ intrathecal dosage was 900 mg every two weeks.
  - Part C (NCT04958642) was an open-label extension that enrolled 66 patients including 35 LEMBAZ-treated patients from Parts A and B, 18 treatment-naïve, and 13 LEMBAZ-treated patients from Trial 2. The LEMBAZ dosage was 900 mg intrathecally every two weeks.
- Trial 2 (NCT01747135) was a 78-week, non-randomized, open-label, single-center cohort, dose escalation trial that enrolled a total of 14 patients between 4 and 23 years of age with neurological manifestations of

NPC. LEMBAZ was administered intrathecally at a dosage that ranged from 200 to 1,200 mg once monthly (these dosage regimens are not recommended *[see Dosage and Administration (2.2)]*), with patients up-titrated based on tolerability and efficacy.

- Trial 3 (NCT03643562) was a non-randomized, open-label, single-arm trial that enrolled 27 patients (9 treatment-naïve, 18 previously treated through expanded access program) with neurological manifestations of NPC between 4 and 43 years of age. Treatment-naïve patients started at LEMBAZ 400 mg intrathecally every two weeks, while patients already receiving LEMBAZ continued at their current stable dosage intrathecally every two weeks. The Trial 3 duration was open-ended; mean (SD) duration of LEMBAZ treatment was 75 (36) weeks.
- The expanded access program data included 85 patients with neurological manifestations of NPC between 1 and 43 years of age (mean age was 12 years) who were treatment-naïve (71 patients) or previously treated (14 patients) under Trials 1, 2, and 3. Treatment-naïve patients were dosed intrathecally every two weeks at a starting intrathecal LEMBAZ dosage of 200 mg (less than 4 years of age) or 400 mg (4 years of age or older). The LEMBAZ dosage was increased to a maximum of 600 mg (for patients who weighed 7 to 12 kg) or 900 mg (for patients who weighed more than 12 kg) every two weeks. Patients already receiving LEMBAZ continued at their current stable dosage. The duration of the expanded access program was open-ended; mean (SD) duration of treatment with LEMBAZ was 44 (32) months.
- Study 1 is an observational, prospective, natural history study of patients with NPC regardless of age or age of neurological manifestation onset. A total of 44 control patients with NPC whose neurological manifestations started prior to 6 years of age from Study 1 were eligible for matching to LEMBAZ-treated patients in the integrated survival analysis.

Thirty-six (36) LEMBAZ-treated patients with NPC with neurological manifestations that started at less than 6 years of age from Trials 1, 2, 3, and the expanded access program were matched to external control patients with NPC from Study 1. Matching was based on disease subtype (early vs. late infantile-onset), age of neurological symptom onset (±3 months), and baseline miglustat use (yes vs. no) using a many-to-one matching algorithm. The matching also required the matched untreated patient from Study 1 to be alive at the age that the treated patient started LEMBAZ treatment (referred to as the index age for a matched stratum). Of the 36 LEMBAZ-treated patients, 11, 2, 2, and 21 patients originally started LEMBAZ treatment in Trials 1, 2, 3, and the expanded access program, respectively. The survival time was calculated as the time between the index age and the age of last follow-up or death. All studies allowed the concomitant use of miglustat.

Efficacy Results

In both the LEMBAZ-treated group and the external control group, the mean index age was 5.7 years (range: 1 to 19 years). In both groups, most patients were White (94%); 58% of the LEMBAZ-treated patients were male and 33% of the external control patients were male; 67% of the patients had early infantile-onset NPC in both groups; 50% of the patients were concomitantly treated with miglustat at baseline in both groups.

Median survival follow-up time from the index age was 5.6 years (range: 1.6 months to 9.2 years) in the LEMBAZ-treated group and 4.2 years (range: 2.5 months to 13.8 years) in the external control group. LEMBAZ-treated patients were exposed to LEMBAZ for a median duration of 3.6 years (range: 1.4 months to 8.7 years). The median final LEMBAZ dosage among the treated patients was 750 mg (range: 300 to 1,050 mg) (the maximum recommended dosage is 900 mg every two weeks).

LEMBAZ-treated patients had longer overall survival compared to the matched external control group, with a 55% reduction in the risk of death (Table 8 and Figure 1). Longer overall survival was observed independent of baseline miglustat use.

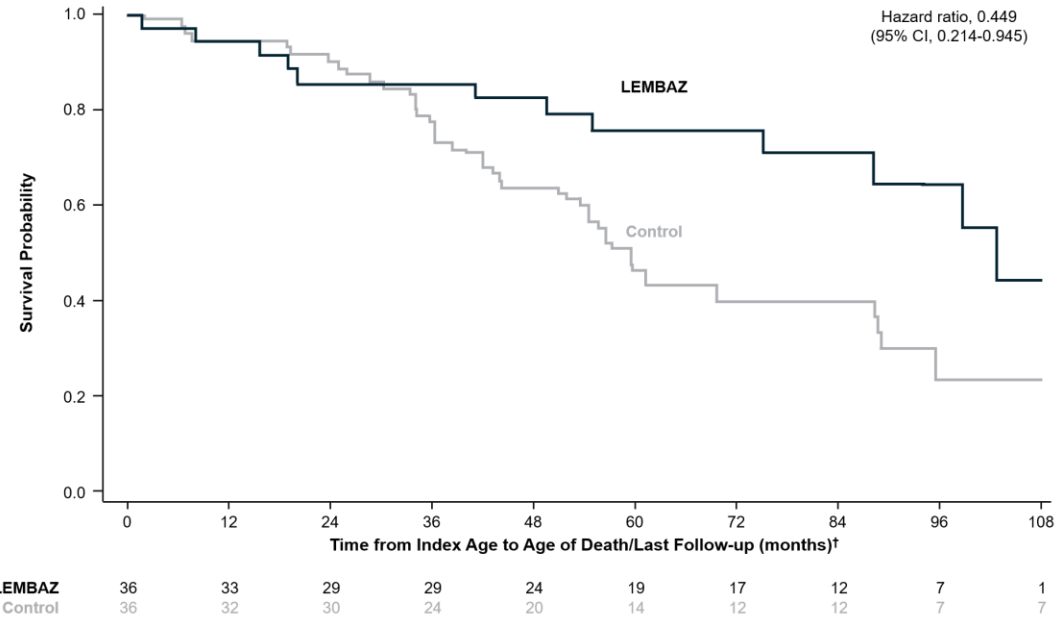
Table 8: Overall Survival in LEMBAZ-Treated Patients with NPC Whose Neurological Manifestations Started Prior to 6 Years of Age vs. Untreated Patients with NPC (Matched External Control)

	LEMBAZ (N=36)	**External Control (N=36)***
Number of deaths (%)†	12 (33.3%)	24 (66.9%)
Median survival time in months†	102	59
Hazard ratio for risk of death (95% CI)‡	0.45 (0.21, 0.95)	

CI = Confidence interval

*The analysis included a total of 26 patients in the external control group from Study 1. Control patient data were weighted by the inverse of the total number of matched controls of the LEMBAZ-treated patient. The weighted number of control patients was 36.
†Estimated from weighted Kaplan-Meier method up to the maximum follow-up time (110 months) in the LEMBAZ-treated group.
‡Hazard ratio (95% CI) was generated from a weighted Cox regression model including treatment (LEMBAZ-treated vs. matched controls) as fixed effect, and baseline miglustat as a covariate.

Figure 1: Kaplan-Meier Curves for Overall Survival in LEMBAZ-Treated Patients with NPC Whose Neurological Manifestations Started Prior to 6 Years of Age vs. Untreated Patients with NPC (Matched External Control)*



*The survival curves were estimated from weighted Kaplan-Meier method up to the maximum follow-up time (110 months) in the LEMBAZ-treated group. The number at risk for the external control group from Study 1 is the rounded integer value of the total sum of the weights for patients at risk.
†The index age was defined as age at initiation of LEMBAZ treatment for a LEMBAZ-treated patient and its matched control patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

LEMBAZ (adrabetadex) injection is supplied as a clear, colorless, preservative-free, sterile solution in a single-dose vial for intrathecal use.

NDC Number	Strength	Package
Carton: 87230-101-01 Vial: 87230-101-02	900 mg/4.5 mL (200 mg/mL)	One single-dose vial in a carton

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30ºC (59°F to 86ºF) [see USP Controlled Room Temperature]. Do not refrigerate. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Hearing Impairment Including Permanent Hearing Loss

Advise patients and/or their caregivers about the risks of permanent hearing impairment with LEMBAZ treatment, and that comprehensive audiology evaluations should be performed before and during treatment *[see Warnings and Precautions (5.1)]*.

Ataxia

Advise patients and/or their caregivers that ataxia may occur after LEMBAZ administration *[see Warnings and Precautions (5.2)]*.

Fatigue

Advise patients and/or their caregivers that fatigue may occur after LEMBAZ administration *[see Warnings and Precautions (5.3)]*.

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