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For further information regarding Indication and Important Safety Information for DAYBUE, please click here: [Prescribing Information](#).

DAYBUE™ (trofinetide): Management of Diarrhea Adverse Events

This letter is provided in response to your specific request for information regarding the management of diarrhea adverse events in patients receiving trofinetide. In the pivotal trial, LAVENDER™, the management of diarrhea was not protocolized, and was conducted per the discretion of the site primary investigator.

This document provides information from the product labeling, the approach that was used in the LAVENDER trial, and more methods based on expert consensus articles published in June 2023 and June 2024, and a caregiver/nurse perspectives article published in 2024. Always use clinical judgment as you consider these management strategies.

Relevant Labeling Information¹

- **Warnings and Precautions**

- In LAVENDER and in long-term studies, 85% of patients treated with DAYBUE experienced diarrhea. In those treated with DAYBUE, 49% either had persistent diarrhea or recurrence after resolution despite dose interruptions, reductions, or concomitant antidiarrheal therapy. Diarrhea severity was of mild or moderate severity in 96% of cases. In LAVENDER, antidiarrheal medication was used in 51% of patients treated with DAYBUE.

Advise patients to stop laxatives before starting DAYBUE. If diarrhea occurs, patients should notify their healthcare provider, consider starting antidiarrheal treatment, and monitor hydration status and increase oral fluids, if needed. Interrupt, reduce dose, or discontinue DAYBUE if severe diarrhea occurs or if dehydration is suspected.

Summary

- [Recommendations for diarrhea management](#) are included in the label for prescribers to consider when prescribing trofinetide.¹
- To manage the diarrhea associated with trofinetide in the LAVENDER™ Phase 3 study,² a [management plan](#) was developed at the Children's Hospital of Philadelphia and was provided to the clinical trial sites while the Phase 3 study was ongoing.³
 - This diarrhea [management plan](#) included recommendations for the discontinuation or adjustment of bowel medications for constipation as well as administration of psyllium fiber and loperamide, with adjustments based on the individual's bowel movement frequency and consistency.³
 - These recommendations were not protocolized or required.⁴
- Practical recommendations for the management of diarrhea in individuals with RTT using trofinetide, based on [expert opinion](#) and [caregiver/nurse perspectives](#), are available.⁵⁻⁷

Recommendations from the Product Label

Advise patients to stop laxatives before starting trofinetide. If diarrhea occurs, patients should notify their healthcare provider, consider starting antidiarrheal treatment, and monitor hydration status and increase oral fluids, if needed. Interrupt, reduce dose, or discontinue trofinetide if severe diarrhea occurs or if dehydration is suspected.¹

Management of Diarrhea Adverse Events in the LAVENDER Phase 3 Study

The 12-week Phase 3 LAVENDER study evaluated the efficacy and safety of trofinetide vs. placebo in 187 female participants (5–20 years old) with RTT.² During the trial, although data were blinded, it was noticed that a significant portion of participants were reporting diarrhea. To manage the diarrhea, a management plan was developed at the Children’s Hospital of Philadelphia and was provided to the clinical trial sites while the Phase 3 study was ongoing.³ These recommendations were not protocolized or required.⁴ The effectiveness of this plan for the management of diarrhea associated with trofinetide has not been determined.

Children’s Hospital of Philadelphia Diarrhea Management Plan

This diarrhea management plan included recommendations for the discontinuation or adjustment of bowel medications for constipation as well as administration of psyllium fiber and loperamide, with adjustments based on the individual’s bowel movement frequency and consistency.³

The recommendations were the following:

1. Stop all bowel medications the day the participant is randomized. If no diarrhea occurs during double-blind treatment, hold all bowel medications the first day of open-label dosing.
2. Ask caregivers to contact the coordinator at the first episode of diarrhea, even if it is just softening of stool. Do not wait for the stool to become watery.
3. At the onset of diarrhea, immediately start loperamide and psyllium fiber. Tell caregivers to use the loading dose of loperamide (which is usually 15 mL), then have them use the secondary dose daily (which is usually 7.5 mL). The psyllium fiber is daily and dosed per the packaging instructions.
4. If there is no bowel movement for 2 to 3 days, hold the loperamide until a bowel movement occurs, then use the loperamide as needed until the subject displays a good balance.
5. Psyllium fiber continues even if the diarrhea resolves.
6. A diet of cereal or bananas, rice, applesauce, and toast may help with the diarrhea as well.

Note: If the subject stops all their regular bowel medications and does NOT have diarrhea or a bowel movement for 2 to 3 days, resume all their normal bowel medications so the subject does not become constipated.

Expert Opinion

Practical recommendations for the management of diarrhea in individuals with RTT using trofinetide, as developed by experts in gastroenterology and RTT, are shown in **Table 1**.^{5,6}

Table 1. Expert Recommendations for Diarrhea Management for Individuals Being Treated with Trofinetide^{5,6}

Prior to initiating trofinetide	
1	Explain the possibility of diarrhea to families as part of a risk-benefit discussion
2	Obtain a 7-day baseline of bowel activity (stool frequency and consistency, presence of blood) and provide caregiver education on diarrhea management
Upon initiation of trofinetide	
3	Upon the start of trofinetide, stop or reduce all constipation medications
4	At initiation of trofinetide, examine any concomitant medications and switch as many liquid medications that contain sugar alcohols as possible to pill form
5	<p>Start fiber (e.g. psyllium, wheat dextrin, flaxseed) as a stool normalizer when starting trofinetide according to the following dosing instructions:</p> <ul style="list-style-type: none"> • Children: 0.5–1 tsp 1–3 times daily in 4 oz water • Adolescents/adults: 1–2 tsp 1–4 times daily in 8 oz water <p>Continue fiber to promote bowel health, even in the absence of diarrhea or if diarrhea resolves</p>
6	<p>An approach to mitigate diarrhea could be to initiate trofinetide at a lower dose and gradually titrate up to a higher dose over the course of several weeks.</p> <ul style="list-style-type: none"> ○ Clinicians are encouraged to follow their patients for a longer period of time (at least 6 months) to find a dose that balances tolerability and treatment benefits
Upon occurrence of diarrhea	
7	<p>At the onset of diarrhea, start oral loperamide according to the following dosing instructions:</p> <ul style="list-style-type: none"> • Children 2–<12 years of age: <ul style="list-style-type: none"> ○ 2–5 years of age and/or weighing 13–<21 kg: initially 1 mg with first loose stool, followed by 1 mg/dose every 8 hours; maximum: 3 mg/day ○ 6–8 years of age and/or weighing 21–27 kg: initially 2 mg with first loose stool, followed by 1 mg/dose every 8 hours; maximum: 4 mg/day ○ 9–11 years of age and/or weighing 27.1–43 kg: initially 2 mg with first loose stool, followed by 1–2 mg/dose every 8 hours; maximum: 6 mg/day • Children ≥12 years of age and adolescents weighing >43 kg: <ul style="list-style-type: none"> ○ Initially 4 mg with first loose stool, followed by 2 mg/dose every 8 hours; maximum: 8 mg/day • Adults: <ul style="list-style-type: none"> ○ Initially 4 mg with first loose stool, followed by 4 mg/dose every 6 hours; maximum: 16 mg/day • Use the lowest effective dose of loperamide that maintains symptomatic control • If no bowel movement occurs for 24 hours, withhold loperamide until a bowel movement occurs • If bloody diarrhea occurs, loperamide is contraindicated and should not be used • Other antidiarrheal medications to consider include bismuth subsalicylate and cholestyramine; anticholinergic medication may be considered for severe cramping. Consult with the individual's gastroenterologist
8	<p>If diarrhea occurs, ask the caregiver to contact the prescriber and to begin tracking the consistency and frequency of bowel movements or the occurrence of new fecal incontinence. If diarrhea persists despite the discontinuation of constipation medications and the initiation of fiber supplements and anti-diarrheal medications, consider:</p> <ul style="list-style-type: none"> ○ A 50% dose reduction of trofinetide. Following resolution of the diarrhea, trofinetide may be titrated back up to the full dose ○ Reducing trofinetide dose to previous dose used prior to the occurrence of diarrhea ○ Dividing the dose from twice daily to 3–4 times per day ○ Feed rice cereal along with trofinetide
Other	
9	<ul style="list-style-type: none"> • Initiate the following dietary and hydration measures: • Diet

- For a child who is not dehydrated, continue a regular diet
- Regular milk, yogurt, complex carbohydrates (e.g. bread, potatoes, rice, wheat), fruits, vegetables, and lean meats are recommended
- High-fat foods should be avoided
- Food should be provided in smaller and more frequent volumes
- Fruit juice should be given at half-strength (i.e. mixed with an equal amount of water)
- Hydration
 - Review daily fluid requirements and intake in light of potential increased fluid output due to diarrhea
 - Monitor for dehydration
 - Signs of mild dehydration include increased thirst, a slightly dry mouth, and slightly decreased urination
 - Signs of moderate or severe dehydration include dry mouth, significantly decreased urination, lack of tears, and sunken eyes
 - Administer an oral rehydration solution (e.g. Pedialyte® or generic) for mild dehydration
 - 5 tsp/lb should be given over 4 hours
 - Small volumes of the dose can be given as frequently as every few minutes or as tolerated
 - Contact the prescriber in the event of moderate or severe dehydration

10	If the individual has stopped constipation medications and does not have diarrhea or a bowel movement for 24 hours, regular constipation medications may be resumed as needed
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Caregiver and Nurse Perspectives

Practical tips for the management of diarrhea resulting from trofinetide treatment from five caregivers whose daughters participated in trofinetide clinical trials are shown in **Table 2**.⁷

Table 2. Practical Tips for Caregiver Management of Trofinetide-induced Diarrhea⁷

Preventing dehydration	
<ul style="list-style-type: none"> • Powdered packets of Pedialyte (allows for as-needed use) • Protein water 	
Packing supplies for trips	
<ul style="list-style-type: none"> • Extra clothes • Disposable underpads • Diapers • Wipes (larger preferred) • Cleaning supplies • Gloves • Trash bags • Scissors • For those with a feeding tube: Supplies for bolus administration of water, Pedialyte, Imodium • “If you think you have enough supplies, grab more” 	
Preparing areas for cleanup, diaper changes	
<ul style="list-style-type: none"> • Laying towels over the car seat • Bedding: Make several layers of full bed-sized disposable underpads with a sheet on top (allows for removal of the top sheet/disposable underpad if soiled, with a clean layer underneath) • Van: Something to lay down in the back for changing, such as a folding tumbling mat, folding massage table, curtain for privacy <ul style="list-style-type: none"> ○ Several caregivers noted that public changing stations, especially for larger children/adolescents, are difficult to find. Those that do exist are often in women’s restrooms, making it difficult for male caregivers to access 	
Clearing/preventing diaper rash	
<ul style="list-style-type: none"> • After cleaning up diarrhea, use a hair dryer to dry the area and then apply Aquaphor, Desitin, or Butt Paste (any or all combined) 	

References

1. DAYBUE™ (trofinetide) [package insert]. San Diego, CA. Acadia Pharmaceutical Inc. [\[Link\]](#)
2. Neul JL, Percy AK, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study. *Nat Med*. 2023;29(6):1468-1475. [\[PubMed\]](#)
3. Acadia Pharmaceuticals Inc. Data on File. ACP-2566-003 Clinical Study Report. 2022.
4. Acadia Pharmaceuticals Inc. Data on File. ACP-2566-003 Protocol. 2020.
5. Marsh ED, Beisang A, Buie T, Benke TA, Gaucher B, Motil KJ. Recommendations for the management of diarrhea with trofinetide use in Rett syndrome. *Expert Opinion on Orphan Drugs*. 2023;11(1):1-8. [\[Link\]](#)
6. Motil KJ, Beisang A, Smith-Hicks C, Lembo A, Standridge SM, Liu E. Recommendations for the management of gastrointestinal comorbidities with or without trofinetide use in Rett syndrome. *Expert Rev Gastroenterol Hepatol*. 2024;18(6):227-237. [\[PubMed\]](#)
7. Moore R, Poulsen J, Reardon L, et al. Managing Gastrointestinal Symptoms Resulting from Treatment with Trofinetide for Rett Syndrome: Caregiver and Nurse Perspectives. *Adv Ther*. 2024;41(4):1305-1317. [\[PubMed\]](#)