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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, methods based on an expert consensus article published in June 2024, and a caregiver/nurse perspectives article published in 2024. Always use clinical judgment as you consider these management strategies.

Relevant Label 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
- Practical recommendations for the management of diarrhea in individuals with RTT using trofinetide, based on [expert opinion](#) and [caregiver/nurse perspectives](#), are available.²⁻⁴

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

Expert Opinion

Practical recommendations published in June 2024 for the management of diarrhea in individuals with RTT using trofinetide, as developed by experts in gastroenterology and RTT, are shown in

Table 1.² Additional guidance on managing trofinetide-associated diarrhea is available in an expert consensus article by Marsh et al., published in June 2023.³

Table 1. Expert Recommendations for Diarrhea Management for Individuals Being Treated with Trofinetide²

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 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	Start fiber (e.g., psyllium, pectin, wheat dextrin, flaxseed) as a stool normalizer when starting trofinetide
6	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. ○ 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	At the onset of diarrhea, start an anti-diarrheal medication
8	Ask the caregiver to begin tracking the consistency and frequency of bowel movements. If diarrhea persists despite the discontinuation of constipation medications and the initiation of fiber supplements and anti-diarrheal medications, consider: ○ 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	• Initiate the following dietary and hydration measures: • Diet ○ For a child who is not dehydrated, continue a regular diet • Hydration ○ Monitor for 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

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.**⁴

Table 2. Practical Tips for Caregiver Management of Trofinetide-induced Diarrhea⁴

Preventing dehydration	
• Powdered packets of Pedialyte (allows for as-needed use) • Protein water	
Packing supplies for trips	
• 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

- 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
 - 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

- 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 Pharmaceuticals Inc. [\[Link\]](#)
2. 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. [\[PubMed\]](#)
3. 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. [\[Link\]](#)
4. 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. [\[PubMed\]](#)