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For further information regarding Indication and Important Safety Information for DAYBUE and DAYBUE STIX, please click here: Prescribing Information.

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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, recommendations from an expert consensus using a modified Delphi method, and practical guidance from 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 Information[1]

- **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 or DAYBUE® STIX (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 DAYBUE or DAYBUE STIX 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]
- Recommendations on assessing and managing trofinetide tolerability are available from an **expert consensus** on real-world use of trofinetide using a modified Delphi method.[2]
- Practical recommendations for the management of diarrhea in individuals with RTT using trofinetide, based on **expert opinion** and **caregiver/nurse perspectives**, are available.[3-5]

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 Consensus on Real-World Use of Trofinetide Using a Modified Delphi Method

A modified Delphi process was conducted in the United States to establish consensus recommendations for the practical use of trofinetide in the treatment of RTT. This modified Delphi method involved the development and refinement of a set of 72 statements by a multidisciplinary steering group of five trofinetide-experienced RTT experts practicing at US RTT Centers of Excellence, followed by assessment and rating of the statements by a panel of trofinetide-experienced RTT experts also practicing at a US RTT Centers of Excellence. Two rounds of assessments were completed by 25 respondents in each round, resulting in consensus (i.e. 75% agreement) being reached across the final statement set.[2] This differs from the standard Delphi process where all statements are generated by the entire group of participants, and the process is strictly survey-based.[6]

The consensus recommendations include the pre-treatment assessment of gastrointestinal function and caregiver counseling on potential side effects as part of the pre-trofinetide assessments and counseling, as outlined in **Table 1**.[2]

Table 1. Selected Consensus Statements Relating to Pre-Trofinetide Assessments and Counseling[2]

Statement:	Strongly agree	Tend to agree	Tend to disagree	Strongly disagree	Overall agreement
Patient history of bowel activity, vomiting and nutritional status should be obtained prior to initiating trofinetide, to help individualize bowel management	80%	20%	0%	0%	**100%**
Consider discontinuing all constipation medications prior to initiating trofinetide	48%	36%	16%	0%	**84%**
Consider decreasing the dose of all constipation medications prior to initiating trofinetide, as deemed appropriate based on the individual patient	48%	44%	8%	0%	**92%**
Counsel patients and/or caregivers that potential side effects may occur (diarrhea and vomiting) and guidance for managing them	96%	4%	0%	0%	**100%**

In addition, the consensus recommendations support the management of side effects with dose adjustments, pauses, and other interventions prior to discontinuation, as outlined in **Table 2**.[2]

Table 2. Selected Consensus Statements Relating to Assessing and Managing Trofinetide Tolerability[2]

Statement:	Strongly agree	Tend to agree	Tend to disagree	Strongly disagree	Overall agreement
Reducing a patient's trofinetide dose to a level at which side effects can be managed, or pausing and restarting on a lower dose with the intention to increase as tolerated, is preferable to stopping the dose entirely	72%	28%	0%	0%	**100%**
For patients experiencing severe side effects, their dosage should be reduced to a level at which they no longer experience side effects	88%	12%	0%	0%	**100%**

Statement:	Strongly agree	Tend to agree	Tend to disagree	Strongly disagree	Overall agreement
Should any side effect require dose reduction, the side effect should be carefully managed until it is safe to increase the dose again	80%	20%	0%	0%	**100%**
For patients experiencing severe and/or persistent side effects, healthcare providers should consider alternative underlying causes not related to trofinetide (e.g. diet, other medications)	36%	60%	0%	4%	**96%**
The healthcare provider should adapt the titration schedule first before introducing additional medications, such as Imodium, to manage diarrhea	52%	28%	20%	0%	**80%**
Fibrous foods such as bananas, peanut butter, avocado or fiber bars may be used to manage diarrhea	60%	36%	4%	0%	**96%**
For those receiving nutrition through gastrostomy, consider switching to an alternative brand of formula or a blenderized diet to improve digestive tolerance and manage diarrhea	32%	44%	20%	4%	**76%**
If a patient's stool becomes "peanut butter consistency", they should be encouraged to increase their fiber intake	32%	44%	24%	0%	**76%**
Imodium may be considered short-term (i.e., a few days) to manage severe diarrhea, but only if other options are unsuitable or ineffective, and should be discontinued as soon as clinically appropriate	48%	32%	12%	8%	**80%**
Ongoing monitoring and management of bowel activity is important, as patients may develop or redevelop constipation after their body adjusts to prolonged use of trofinetide	64%	36%	0%	0%	**100%**
Despite trofinetide's risk of diarrhea, maintaining adequate hydration and routinely monitoring bowel activity are important to prevent or minimize development or redevelopment of constipation as their body adjusts to trofinetide	80%	20%	0%	0%	**100%**

Not all of the consensus recommendations are consistent with the FDA-approved Prescribing Information for DAYBUE. For example, the efficacy of trofinetide has only been demonstrated at the FDA-recommended weight-based dose. Improvements may not occur until patient reaches the recommended dose and continues treatment. The Delphi consensus process was supported by Acadia Pharmaceuticals Inc. All steering group members received honoraria from Acadia while undertaking this work.

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 3**.[3] Additional guidance on managing trofinetide-associated diarrhea is available in an expert consensus article by Marsh et al., published in June 2023.[4]

Table 3. Expert Recommendations for Diarrhea Management for Individuals Being Treated with Trofinetide[3]

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 4**.[5]

Table 4. Practical Tips for Caregiver Management of Trofinetide-induced Diarrhea[5]

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. Prange EOC, Beisang A, Pehlivan D, Suter B, Schleifer P. Expert Consensus on Real-World Use of Trofinetide for Rett Syndrome Using a Modified Delphi Method. *Annals of the Child Neurology Society.* 2026;4(1):38-51. **[Link]**
3. 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]**
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5. 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]**
6. Varndell W, Fry M, Elliott D. Applying real-time Delphi methods: development of a pain management survey in emergency nursing. *BMC Nurs.* 2021;20(1):149. **[PubMed]**