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

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DAYBUE® (trofinetide) Drug-Drug Interactions

This letter is being provided based on your specific request for information on the drug-drug interactions with trofinetide.

Acadia Pharmaceuticals Inc. is unable to provide a comprehensive list of medications that have the potential to interact with trofinetide. As new products are continually emerging in the US market, Acadia cannot ensure the accuracy of such a listing. For more information regarding the medications listed, please refer to the FDA-approved labeling or manufacturer.

Summary

- The following information on drug-drug interactions with trofinetide is available:
  - Information from the product label
  - Potential for drug-drug interactions at target clinical concentrations
  - In vivo drug interaction study of loperamide
  - Examples of clinical substrates for cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)

Information on Drug-drug Interactions from the Product Label

Effect of DAYBUE on Other Drugs

CYP3A and/or P-gp Substrates

Closely monitor patients when DAYBUE is administered concomitantly with sensitive CYP3A and/or P-gp substrates where minimal increases in the plasma concentration of these substrates may lead to serious adverse reactions. Trofinetide, a weak inhibitor of CYP3A and an inhibitor of P-gp, increased the plasma concentrations of CYP3A and/or P-gp substrates, which may increase the risk of adverse reactions associated with these substrates.[1]

Drug Interaction Studies

Clinical Studies

CYP3A and/or P-gp Substrates:

Coadministration of trofinetide 12,000 mg twice daily with 4 mg of loperamide (a moderately sensitive CYP3A substrate and a P-gp substrate) increased the AUC of loperamide by 1.73-fold and the C_{max} by 1.95-fold. Administration of trofinetide 2 hours prior to loperamide increased the AUC of loperamide by 1.22-fold and the C_{max} by 1.44-fold.[1]

In Vitro

Trofinetide is not a substrate of CYP450 enzymes, uridine diphosphate glucuronosyltransferase (UGT), or major drug transporters.[1]

Cytochrome P450 (CYP450) Enzymes:
Trofinetide inhibits CYP3A. Trofinetide inhibits CYP1A2, 2B6, 2C8, 2C19, and 2D6, but is not expected to result in clinically significant drug interactions. Trofinetide does not inhibit CYP2C9.[1]

UDP-Glucuronosyltransferase (UGT):
Trofinetide inhibits UGT enzymes, UGT1A9, 2B7, and 2B15.[1]

Transporter Systems:
Trofinetide inhibits P-gp, BCRP, and BSEP. Trofinetide inhibits OAT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K, but is not expected to result in clinically significant drug interactions. Trofinetide does not inhibit OAT3.[1]

Potential for Drug-Drug Interactions at Target Clinical Concentrations

The maximal systemic plasma concentrations in the orally dosed clinical studies for trofinetide were significantly lower than the IC_{50}s measured for the CYP enzymes and the renal and hepatic drug transporters studied. Consequently, the potential is low for clinically relevant systemic drug-drug interactions mediated by trofinetide CYP inhibition, CYP induction, or renal and hepatic drug transporter inhibition, which would increase the plasma concentration of co-administered drugs that are metabolized by CYP enzymes or are substrates of renal and hepatic drug transporters. The intestinal concentration of trofinetide following oral administration at the clinical dose of 12 g twice daily is approximately 152 mM. Given the measured IC_{50}s, trofinetide has the potential for inhibitory interactions in the intestine that would increase the absorption of co-administered drugs that have low bioavailability and are significant CYP3A4 substrates or substrates of the P-gp and/or breast cancer resistance protein (BCRP) drug transporters.[2]

In Vivo Drug Interaction Study of Loperamide

ACP-2566-012 was an open-label, Phase 1 study in 15 healthy adults to assess the effect of trofinetide on the pharmacokinetic (PK) profile of loperamide and to evaluate the safety and tolerability of trofinetide when administered in combination with loperamide. Three treatment cycles were assessed sequentially over a 12-day period: a single 4 mg dose of loperamide administered alone, concomitantly with the first dose of 12 g BID trofinetide, or 2 hours after the first dose of trofinetide in healthy adult subjects (**Table 1**). PK blood sampling and electrocardiograms (ECGs) were conducted at baseline and throughout the treatment period.[3]

Table 1. Study Drug Administration Schedule (ACP-2566-012 Treatment Period)[3]

	Day 1	Days 2–4	Day 5	Days 6–8	Day 9	Days 10–11*
Loperamide 4 mg (single dose)	✓	–	✓	–	✓	–
Trofinetide 12 g BID†	–	–	✓ (1st dose concomitantly with loperamide)	✓	✓ (1st dose 2 hours prior to loperamide)	✓

**Study assessments were conducted from Day 1 through Day 12. EOT procedures occurred on Day 12.*
†The second dose of trofinetide 12 g was administered at least 8 hours (and up to 10 hours) following the first trofinetide dose.
Abbreviations: BID=twice daily; EOT=end of treatment.

Pharmacokinetic Results

Concomitant administration of loperamide with trofinetide increased the C_{max} (by 1.9-fold) and extent of absorption (as measured by AUC_{0-t} [by 1.8-fold] and $AUC_{0-\infty}$ [by 1.7-fold]) of loperamide compared to loperamide administered alone. Delaying administration of loperamide until 2 hours after trofinetide reduced the impact on C_{max} (1.4-fold) and on extent of absorption (AUC_{0-t} [1.3-fold] and $AUC_{0-\infty}$ [1.2-fold]) of loperamide.[3]

ECG Results

Loperamide alone (Day 1) or concomitantly with trofinetide (Day 5 and Day 9) did not have a clinically relevant effect on heart rate or on cardiac conduction (i.e., PR and QRS intervals). The effect on cardiac repolarization (QT interval) of loperamide when administered alone (Day 1) or concomitantly with trofinetide (Day 5 and Day 9) demonstrated that an effect on both ΔQTcF and ΔΔQTcF exceeding 10 ms can be excluded within the full observed range of loperamide and its metabolite, N-desmethyl loperamide, concentrations up to ~2.17 ng/mL and ~1.8 ng/mL, respectively.[3]

Safety Results

There were no unexpected safety findings with trofinetide oral 12 mg BID administered alone or in combination with single 4 mg oral doses of loperamide to healthy adult participants. Overall, 10 subjects (66.7%) reported at least one treatment-emergent adverse event (TEAE) in the study (**Table 2**). There was one TEAE of atrioventricular block second degree reported in 1 subject (6.7%), which led to drug being withdrawn. The TEAE was mild in severity and considered not related to study drug (either loperamide, trofinetide, or both), and the TEAE resolved.[3]

Table 2. Overall Summary of TEAEs – Safety Analysis Set (N=15)[3]

	Loperamide, n (%)	Loperamide + TROF, n (%)	Loperamide 2 hours after TROF, n (%)	Overall, n (%)
Any TEAE	5 (33.3)	8 (53.3)	9 (60.0)	10 (66.7)
Any serious TEAE	0	0	0	0
Any TEAE related to loperamide	2 (13.3)	1 (6.7)	1 (6.7)	2 (13.3)
Any TEAE related to TROF	0	1 (6.7)	2 (13.3)	2 (13.3)
Any TEAE related to loperamide and TROF	0	1 (6.7)	0	1 (6.7)
Any TEAE leading to discontinuation of study drug	1 (6.7)	0	0	1 (6.7)
Any TEAE leading to death	0	0	0	0

Abbreviations: TEAE=treatment-emergent adverse event; TROF=trofinetide.

Overall, the most common TEAEs (reported in ≥2 participants) were dermatitis contact reported by 6 (40.0%) participants, constipation reported by 2 (13.3%) participants, and diarrhea reported by 2 (13.3%) participants. All other TEAEs were reported by 1 (6.7%) participant each.[3]

Examples of Clinical Substrates for CYP3A4 and P-gp

Table 3 provides examples of sensitive and moderate sensitive clinical substrates for CYP3A4, as listed by the US Food and Drug Administration (FDA). Please note, CYP3A4 is the major isoform of CYP3A.[4] Other CYP3A isoforms (3A5, 3A7, and 3A43) are not included in the FDA's CYP enzyme- and transporter system-based clinical substrates, inhibitors, or inducers.[5]

Table 3. Examples of Sensitive and Moderate Sensitive Clinical Substrates for CYP3A4[5]

Sensitive substrates[a]			Moderate sensitive substrates[b,c]
alfentanil	felodipine	nisoldipine	alprazolam
avanafil	ibrutinib	quetiapine sildenafil	aprepitant
budesonide	indinavir	simvastatin	atorvastatin
buspirone	ivabradine	sirolimus	colchicine
conivaptan	lemborexant	tacrolimus	eliglustat
darifenacin	lomitapide	ticagrelor	loperamide
darunavir	lovastatin	tipranavir	pimozide
dasatinib	lurasidone	tolvaptan	rilpivirine
dronedarone	maraviroc	triazolam	rivaroxaban
eletriptan	midazolam	vardenafil	tadalafil
eplerenone	mobocertinib	venetoclax	
everolimus	naloxegol		

[a]Demonstrate an increase in AUC of ≥5-fold with strong index inhibitors.[5] Trofinetide is a weak CYP3A inhibitor.[1]
[b]Demonstrate an increase in AUC of ≥2- to <5-fold with strong index inhibitors.[5] Trofinetide is a weak CYP3A inhibitor.[1]
[c]Loperamide is a moderately sensitive substrate for CYP3A.[5]
Abbreviation: AUC=area under the curve.

Of the examples of CYP3A4 clinical substrates shown in **Table 3**, buspirone (an anxiolytic) and midazolam (an anti-epileptic) were used as concomitant medications in the pivotal LAVENDER™ study. Buspirone was used concomitantly in 2 (2.2%) participants in the placebo group (N=94) and no participants in the trofinetide group (N=93). Midalozam was used concomitantly in 5 (5.3%) participants in the placebo group and 3 (3.2%) participants in the trofinetide group.[6]

Table 4 provides examples of clinical substrates of P-gp, as listed by the FDA.

Table 4. Examples of Clinical Substrates for P-gp[5]

Substrates	
dabigatran etexilate	fexofenadine
digoxin*	loperamide
edoxaban	

**Has a narrow therapeutic index.[7]*
Abbreviation: P-gp=P-glycoprotein.

Of the examples of P-gp clinical substrates shown in **Table 4**, fexofenadine (an anti-histamine for systemic use) and loperamide (an antidiarrheal) were used as concomitant medications in the pivotal LAVENDER study. Fexofenadine was used concomitantly in 1 (1.1%) participant in the placebo group and no participants in the trofinetide group. Loperamide was used concomitantly in 3 (3.2%) participants in the placebo group (N=94) and 47 (50.5%) participants in the trofinetide group (N=93).[6]

This is not intended to be an exhaustive list and is not a substitute for clinical judgment. Please note that what is considered a ‘small change in plasma concentration’ may vary based on the clinical situation.

References

1. DAYBUE® (trofinetide) [package insert]. San Diego, CA. Acadia Pharmaceuticals Inc. **[Link]**
2. Acadia Pharmaceuticals Inc. Data on File. Trofinetide Investigator's Brochure. March 11, 2025.
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4. Klyushova LS, Perepechaeva ML, Grishanova AY. The Role of CYP3A in Health and Disease. *Biomedicines.* 2022;10(11).
5. FDA. Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers. **[Link]**.
6. Acadia Pharmaceuticals Inc. Data on File. ACP-2566-003 Clinical Study Report. 2022.
7. David MNV, Shetty M. Digoxin. [Updated 2024 Nov 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. **[Link]**.