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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.

The potential of trofinetide to serve as a substrate, inhibitor, or inducer of cytochrome P450 (CYP) enzymes or xenobiotic transporters has been assessed in various *in vitro* assays.[1] There have been no *in vivo* assessments of drug interactions with trofinetide.[2]

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**
  - **Examples of clinical substrates for CYP3A4, OATP1B1 and OATP1B3**

Information on Drug-drug Interactions from the Product Label

Effect of DAYBUE on Other Drugs

Trofinetide is a weak CYP3A4 inhibitor; therefore, plasma concentrations of CYP3A4 substrates may be increased if given concomitantly with DAYBUE. Closely monitor when DAYBUE is used in combination with orally administered CYP3A4 sensitive substrates for which a small change in substrate plasma concentration may lead to serious toxicities.[2]

Plasma concentrations of OATP1B1 and OATP1B3 substrates may be increased if given concomitantly with DAYBUE. Avoid the concomitant use of DAYBUE with OATP1B1 and OATP1B3 substrates for which a small change in substrate plasma concentration may lead to serious toxicities.[2]

Drug Interaction Studies

In Vitro

Trofinetide is not a substrate of CYP450 enzymes, uridine diphosphate glucuronosyltransferase (UGT), or major drug transporters. Therefore, coadministration of drugs that are inducers or inhibitors of CYP450, UGT, or major drug transporters will not significantly affect the systemic exposure of trofinetide.[2]

Trofinetide is a weak CYP3A4 inhibitor. Using physiologically based pharmacokinetic (PBPK) modeling, coadministration of trofinetide with orally administered midazolam, a sensitive CYP3A4 substrate, was predicted to increase the AUC of midazolam by approximately 1.33-

fold. No inhibition on CYP450 enzymes, CYP1A2, 2C8, 2C9, 2C19, and 2D6, is expected at therapeutic systemic concentrations based on the *in vitro* assays and the static mechanistic models. Time-dependent inhibition on CYP2B6 was inconclusive based on *in vitro* data. DAYBUE inhibits UGT enzymes, UGT1A9, 2B7, and 2B15, *in vitro*.[2]

No inhibition was observed at therapeutic systemic concentrations on P-gp, BCRP, BSEP, OAT1, OAT3, OCT2, MATE1, and MATE2-K, based on the in vitro assays. Trofinetide inhibits OATP1B1 and OATP1B3 *in vitro*.[2]

In Vivo
There have been no *in vivo* assessments of drug interactions with trofinetide.[2]

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-glycoprotein (P-gp) and/or breast cancer resistance protein (BCRP) drug transporters.[1]

Examples of Clinical Substrates for CYP3A4, OATP1B1 and OATP1B3

Table 1 provides examples of sensitive and moderate sensitive clinical substrates for CYP3A4, as listed by the US Food and Drug Administration (FDA).

Table 1. Examples of Sensitive and Moderate Sensitive Clinical Substrates for CYP3A4[3]

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

[a]Demonstrate an increase in AUC of ≥5-fold with strong index inhibitors.[3] Trofinetide is a weak CYP3A4 inhibitor.[2]
[b]Demonstrate an increase in AUC of ≥2- to <5-fold with strong index inhibitors.[3] Trofinetide is a weak CYP3A4 inhibitor.[2]
Abbreviation: AUC=area under the curve.

Of the examples of CYP3A4 clinical substrates shown in **Table 1**, buspirone (an anxiolytic) and midazolam (an anti-epileptic) were used as concomitant medications in the pivotal LAVENDER™ study.[4] 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.

Table 2 provides examples of clinical substrates of OATP1B1 and OATP1B3, as listed by the FDA.

Table 2. Examples of Clinical Substrates for OATP1B1/B3[3]

Substrates	
atorvastatin	letermovir
bosentan	paclitaxel
docetaxel	pitavastatin
elagolix	pravastatin
fexofenadine	repaglinide
glecaprevir	rosuvastatin
glyburide	simvastatin
grazoprevir	

Of the examples of OATP1B1/B3 clinical substrates shown in **Table 2**, atorvastatin (a lipid modifying agent) and fexofenadine (an anti-histamine for systemic use) were used as concomitant medications in the pivotal LAVENDER study.[4] Atorvastatin was used concomitantly in 1 (1.1%) participant in the placebo group (N=94) and no participants in the trofinetide group (N=93). Fexofenadine was used concomitantly in 1 (1.1%) participant in the placebo group and no participants in the trofinetide group.

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. Acadia Pharmaceuticals Inc. Data on File. Trofinetide Investigator's Brochure. February 15, 2024.
2. DAYBUE™ (trofinetide) [package insert]. San Diego, CA. Acadia Pharmaceutical Inc. **[Link]**
3. FDA. Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers. **[Link]**.
4. Acadia Pharmaceuticals Inc. Data on File. ACP-2566-003 Clinical Study Report. 2022.