# *Evrysdi Drug Interactions*

This article responds to your request for information on Evrysdi® (risdiplam) and drug interactions.

## In brief

- Evrysdi may increase the plasma concentration of drugs eliminated via MATE1 or MATE2-K, such as metformin.
  - Administration of risdiplam with MATE substrates should be avoided.
  - If co-administration cannot be avoided, it is recommended to monitor for drug-related toxicities and to follow any dose modification recommendations in the product label of the co-administered drug.

## Abbreviations

BRCP=breast cancer resistance protein
CYP=cytochrome P450
DDI=drug-to-drug interaction
FMO1=flavin monooxygenase 1
FMO3=flavin monooxygenase 3
MATE=multidrug and toxin extrusion
MDR1=multidrug resistance protein 1
OAT=organic anion transporter
OATP=organic anion-transporting polypeptide
OCT2=organic cation transporter 2
P-gp=P-glycoprotein

## Enzymes involved in the metabolism of Evrysdi

Evrysdi is primarily metabolized in the liver by the flavin-containing monooxygenases (FMOs) FMO1 and FMO3. It is metabolized to a lesser extent by CYP enzymes 1A1, 2J2, 3A4, and 3A7.

In contrast to the CYP enzymes, FMOs are not readily inhibited or induced by external substances and drug-to-drug interactions (DDIs) are considered rare.[1]

## Effect of Evrysdi on other drugs

### Evrysdi may increase the plasma concentrations of drugs eliminated by MATE1 or MATE2-K.

MATE proteins, mainly MATE1 and MATE-2K, are involved in the active renal secretion, and biliary excretion of various drugs.[2] A comprehensive list of MATE substrates cannot be provided as this is a new field and the literature is constantly evolving.[3] It is recommended to consult the product label of the co-administered drug to check whether it is a MATE1 or MATE2-K substrate.

In vitro, Evrysdi inhibits MATE1 and MATE2-K and has the potential to inhibit these transporters at clinically relevant concentrations.[4,5] The clinical relevance of the co-administration of Evrysdi with MATE1/2-K substrates is unknown.

## No interactions are expected between Evrysdi and drugs eliminated by other transporter proteins.

Evrysdi does not inhibit other drug transporter proteins at clinically relevant concentrations in vitro (Table 1).[5] The induction potential of Evrysdi on transporter proteins has not been studied.[5]

### Table 1. Effect of Evrysdi on other transporter proteins *in vitro*

| Transporter protein | Inhibited by Evrysdi in vitro | Induced by Evrysdi in vitro |
|---|---|---|
| P-gp | No | n/a* |
| BCRP | No | n/a* |
| OATP1B1 | No | n/a* |
| OATP1B3 | No | n/a* |
| OAT1 | No | n/a* |
| OAT3 | No | n/a* |
| OCT2 | No | n/a* |

Notes: *Data not available

## No interactions are expected between Evrysdi and CYP enzyme substrates.

Evrysdi does not inhibit or induce most of the major CYP enzymes (Table 2).

### Table 2. Effect of Evrysdi on CYP enzymes and other transporters *in vitro*

| CYP enzyme | Inhibited by Evrysdi in vitro | Induced by Evrysdi in vitro |
|---|---|---|
| CYP1A2 | No | No |
| CYP2B6 | No | No |
| CYP2C8 | No | No |
| CYP2C9 | No | No |
| CYP2C19 | No | No |
| CYP2D6 | No | n/a* |
| CYP3A4 | Yes, weakly | No |

Notes: *Data not available

Evrysdi is a weak inhibitor of CYP3A4. In healthy adults, administration of Evrysdi slightly increased the exposure of midazolam, a sensitive CYP3A substrate. This increase is not considered to be clinically relevant. A similar increase is expected in children and infants as young as 2 months of age.[4,5]

## Effects of other drugs on Evrysdi

### No interactions are expected between Evrysdi and CYP enzyme inhibitors or inducers.

In healthy volunteers, co-administration of Evrysdi with itraconazole, a strong CYP3A inhibitor, did not have a clinically relevant effect on the pharmacokinetics of Evrysdi.

Co-administration of Evrysdi and CYP enzyme inducers has not been studied.

Overall, the clinical significance of CYP enzyme-mediated DDIs with Evrysdi is expected to be low.[5]

### No significant interaction is expected between Evrysdi and P-gp and BCRP inhibitors or inducers.

In vitro, Evrysdi was a weak substrate of P-gp and BCRP. Due to the high oral bioavailability and in vitro passive permeability of Evrysdi, the clinical significance of P-gp- and BCRP-mediated DDIs is expected to be low.

## Managing potential interactions

Consult the product label of the co-administered drug to check whether it is a MATE1 or MATE2-K substrate. Check whether there are any additional precautions such as additive side effects, for example nausea and vomiting.[4] Concomitant administration of risdiplam with retinotoxic drugs has not been studied and caution is recommended if using together.

### Table 3. Management of potential interactions with Evrysdi

| If the co-administered drug is | then |
|---|---|
| a MATE1 or MATE2-K substrate and co-administration cannot be avoided | monitor for drug-related toxicities and follow any dose modification recommendations for the co-administered medicine. |
| NOT a MATE1 or MATE2-K substrate | monitor for drug-related toxicities. |

## Disclaimer

The decision to prescribe Evrysdi and other medicines concomitantly lies with the physician and should be based on an appropriate assessment of the likely risk-benefit ratio. Appropriate clinical caution and monitoring is recommended. As with all interaction enquiries, we recommend that you also contact the manufacturer of the other non-Roche product.

## References

1. Phillips I, Shephard E. Drug metabolism by flavin-containing monooxygenases of human and mouse. Expert Opin Drug Metab Toxicol 2017;13:167-181. https://www.ncbi.nlm.nih.gov/pubmed/27678284

2. Nies A, Damme K, Kruck S, et al. Structure and function of multidrug and toxin extrusion proteins (MATEs) and their relevance to drug therapy and personalized medicine. Arch Toxicol 2016;90:1555-84. https://www.ncbi.nlm.nih.gov/pubmed/27165417

3. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. . March 10, 2020. Available at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed on June 30, 2023.

4. Roche Internal Regulatory Report (Accessed on 8 August 2023).

5. Risdiplam Monograph. Available at https://didb.druginteractionsolutions.org/drug/monograph/17424/. Accessed on June 30, 2023.