

Givosiran: CYP Enzyme Interactions

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SUMMARY

- An open-label sequential DDI study to evaluate the effect of givosiran on cytochrome P450 activity in the liver was conducted in 10 patients with acute intermittent porphyria.¹
 - There was a differential inhibitory effect on CYP enzymes in the liver shown with givosiran treatment which resulted in a moderate reduction in activity of CYP1A2 and CYP2D6, a minor effect on CYP3A4 and CYP2C19, and a similar weak effect on CYP2C9.¹
- The concomitant use of givosiran with CYP1A2 or CYP2D6 substrates may elevate the concentrations of these substrates, potentially increasing the risk of adverse reactions.²

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CLINICAL DATA

An open-label sequential DDI study to evaluate the effect of givosiran on cytochrome P450 activity in the liver was conducted in 10 patients. Patients who were eligible to participate in the study had an acute intermittent porphyria diagnosis based on a confirmed genetic mutation, with biochemically active disease (defined as having urine PBG levels $\geq 2 \times$ ULN) but who had not experienced acute porphyria attacks within the past 12 months. These patients, referred to as chronic high excretors, had no clinically significant health concerns excluding elevated urine delta-ALA and PBG. Only subjects with wild-type alleles or variant alleles that do not reduce enzyme activity (CYP2C9*1, CYP2C19*1, CYP2D6*1, and CYP2D6*2 alleles) were eligible for participation in the study, as polymorphisms in CYP enzymes could confound data interpretation.^{1,3}

In this study, patients received a single oral dose of a validated cocktail (Inje cocktail) containing 5 probe drugs (5 mg midazolam, 40 mg omeprazole, 200 mg caffeine, 50 mg losartan, and 30 mg dextromethorphan) on Days 1 and 36. Givosiran was administered subcutaneously in a single 2.5 mg/kg dose on Day 8. Relevant plasma concentrations of the Inje cocktail analytes were measured to determine the effect of givosiran on substrates which are specific to the 5 major CYP450 metabolizing enzymes: CYP3A4 (midazolam), CYP2C19 (omeprazole), CYP2C9 (losartan), CYP1A2 (caffeine), and CYP2D6 (dextromethorphan).^{1,3,4}

Pharmacokinetic assessments (blood sample) were conducted immediately before, and at multiple time points within a 24-hour time frame after administration of the Inje cocktail (Days 1 and 36) or givosiran

(Day 8). Pharmacodynamic assessments (urine sample) were collected predose on Days 1, 8, and 36 to quantify changes in *ALAS1* mRNA, ALA, and PBG from baseline. (The predose measurement on Day 8 served as the baseline for *ALAS1*, whereas the measurement on Day 1 was used as the baseline for ALA and PBG).¹

There was a differential inhibitory effect on CYP enzymes in the liver shown with givosiran treatment which resulted in a moderate reduction in activity of CYP1A2 and CYP2D6, a minor effect on CYP3A4 and CYP2C19, and a similar weak effect on CYP2C9.¹

Givosiran has not been investigated in a DDI study with any other medications and any proposed drug interactions would be theoretical and based on the results of the DDI study described above.¹ The use of additional medications that may or may not interact with givosiran is up to the clinical discretion of the prescribing physician.

A more comprehensive list of medications which are metabolized by CYP enzymes can be found on DrugBank webpages (**Table 1**) which is a publicly available online database described in publications.^{5,6}

Table 1. DrugBank List of Medications Metabolized by CYP Enzymes.^{5,6}

CYP Enzymes	DrugBank Webpage
CYP3A4	https://go.drugbank.com/categories/DBCAT002646
CYP2C19	https://go.drugbank.com/categories/DBCAT002638
CYP2C9	https://go.drugbank.com/categories/DBCAT002634
CYP1A2	https://go.drugbank.com/categories/DBCAT002609
CYP2D6	https://go.drugbank.com/categories/DBCAT002623

GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

The DRUG INTERACTIONS section provides the following information²:

Effect of GIVLAARI on Other Drugs

Sensitive CYP1A2 and CYP2D6 Substrates

Concomitant use of GIVLAARI increases the concentration of CYP1A2 or CYP2D6 substrates, which may increase adverse reactions of these substrates. Avoid concomitant use of GIVLAARI with CYP1A2 or CYP2D6 substrates, for which minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP1A2 or CYP2D6 substrate dosage in accordance with approved product labeling.

The CLINICAL PHARMACOLOGY section provides the following information²:

Drug Interaction Studies

Clinical Studies

Effect of givosiran on CYP1A2 Substrates: Concomitant use of a single subcutaneous dose of givosiran 2.5 mg/kg increased caffeine (sensitive CYP1A2 substrate) AUC by 3.1-fold and C_{max} by 1.3-fold.

Effect of givosiran on CYP2D6 Substrates: Concomitant use of a single subcutaneous dose of givosiran 2.5 mg/kg increased dextromethorphan (sensitive CYP2D6 substrate) AUC by 2.4-fold and C_{max} by 2.0-fold.

Effect of givosiran on other CYP450 Substrates: Concomitant use of a single subcutaneous dose of givosiran 2.5 mg/kg increased losartan (CYP2C9 substrate) AUC by 1.1-fold with no change in C_{max} ; increased omeprazole (sensitive CYP2C19 substrate) AUC by 1.6-fold and C_{max} by 1.1-fold; increased midazolam (sensitive CYP3A4 substrate) AUC by 1.5-fold and C_{max} by 1.2-fold. These changes in exposure were not considered clinically relevant.

In-Vitro Studies

Effect of givosiran on CYP450 Enzymes: In vitro studies indicate that givosiran does not directly inhibit or induce CYP enzymes; however, because of its pharmacological effects on the hepatic heme biosynthesis pathway, givosiran has the potential to reduce the activity of CYP enzymes in the liver.

ABBREVIATIONS

ALA = aminolevulinic acid; *ALAS1* = delta-aminolevulinic synthase 1; AUC = area under the curve; C_{max} = maximum serum concentration; CYP = cytochrome P450; DDI = drug-drug interaction; mRNA = messenger ribonucleic acid; PBG = porphobilinogen; ULN = upper limit of normal.

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