Givosiran: Elevations in Blood Homocysteine

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SUMMARY

- Increases in blood homocysteine levels have occurred in patients receiving givosiran. In the OLE of the ENVISION study, blood homocysteine increased was reported in 15 of 93 (16%) patients treated with givosiran.[1]
  - Per the ENVISION clinical study protocol, patients with increased blood homocysteine levels were recommended to receive a supplement containing vitamin B6.[2]
- As the potential risk of long-term exposure to elevated homocysteine is unknown, a publication by Ventura et al (2022) suggests monitoring total plasma homocysteine and homocysteine-related vitamin (B6, B12, and folate) levels before and during givosiran treatment, supplement with vitamins in situations where the homocysteine-related vitamin levels are below normal before initiation or during givosiran treatment, and supplement with vitamin B6 when plasma homocysteine levels are above 100 µmol/L.[3]
- Case reports of elevated homocysteine in patients treated with givosiran have been published in the literature and suggest management to include vitamin B6 supplementation.[4–7]

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GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

The WARNINGS AND PRECAUTIONS section provides the following information[1]:

Blood Homocysteine Increased

Increases in blood homocysteine levels have occurred in patients receiving GIVLAARI. In the ENVISION study, during the open label extension, adverse reactions of blood homocysteine increased were reported in 15 of 93 (16%) patients treated with GIVLAARI. The clinical relevance of the elevations in blood homocysteine during treatment with GIVLAARI is unknown. Measure blood homocysteine levels prior to initiating treatment and monitor for changes during treatment with GIVLAARI. In patients with elevated blood homocysteine levels, assess folate, vitamins B12 and B6. Consider treatment with a supplement containing vitamin B6 (as monotherapy or a multivitamin preparation).

BACKGROUND

Elevations of blood homocysteine can occur due to a variety of factors, including mutations in genes coding for enzymes involved in homocysteine metabolism such as MTHFR or CBS, deficiencies of vitamins that serve as cofactors in the homocysteine metabolic pathway (folate, vitamin B12, or vitamin B6), use of common medications, consumption of alcohol and smoking, and in a variety of diseases such as CKD and inflammatory diseases such as inflammatory bowel disease and lupus, among others.[6–15]

In patients with AHP, elevations in blood homocysteine have also been reported, and a correlation of higher levels of homocysteine is seen in those with greater disease activity. In addition, patients with AHP commonly have deficiencies of vitamins involved in homocysteine metabolism. These deficiencies may be increased in those with greater disease severity. The clinical relevance of homocysteine elevations in patients with AHP is unknown.[5,16,17]

Current evidence supports the possible association between increases in blood homocysteine and givosiran treatment to be attributable to impaired trans-sulfuration pathway catalyzed by CBS. This is evidenced by a strong correlation and co-increase of homocysteine and methionine observed in case reports, as well as the effective reduction of blood homocysteine with supplementation of a CBS cofactor, such as vitamin B6 or heme.[4–7]

CLINICAL DATA

ENVISION Study

The ENVISION study was a phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of givosiran in patients with a documented diagnosis of AHP. Enrolled patients were randomized on a 1:1 basis to receive subcutaneous injections of givosiran 2.5 mg/kg (N=48) or placebo (N=46) once a month for 6 months, followed by an optional 30-month OLE.[18]

In the OLE, patients were initially assigned to givosiran 2.5 mg/kg monthly or givosiran 1.25 mg/kg monthly. A subsequent protocol amendment was enacted to increase the dose for all patients receiving the 1.25 mg/kg monthly dose to the 2.5 mg/kg monthly dose.[18]

Increased blood homocysteine was reported as an AE in a total of 15 patients (16%). Two patients discontinued givosiran treatment because of SAEs of increased blood homocysteine.[18]

Exploratory Plasma Biomarker Assessments in the ENVISION Study

A retrospective, post-hoc analysis of the ENVISION study was conducted to analyze patients' plasma homocysteine levels. Archived serum samples of patients who consented to exploratory biomarker assessment and had baseline samples (N=92) were analyzed.[3]

Plasma homocysteine levels measured during treatment with givosiran in the 6-month double-blind and OLE periods are presented in **Table 1**.[3]

Table 1. Plasma Homocysteine Levels (µmol/L) in the ENVISION Study.[3]

	Baseline	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36
Plasma Homocysteine Level, median (range)	17 (6-158)	85 (7–400)	83 (8–400)	98 (13–400)	47 (14–345)	44 (9–269)	22 (10-207)

Homocysteine elevations were not associated with changes in the efficacy or safety of givosiran. No correlation was found between:[3]

- changes in homocysteine levels at baseline and changes in ALA or PBG levels from baseline and month 6 (Pearson correlation coefficient: -0.068; P=0.54)

- changes in homocysteine and average number of attacks observed during givosiran treatment in patients with and without significant homocysteine elevations
- AEs observed with homocysteine status during givosiran treatment

An additional analysis was conducted analyzing the plasma samples of ENVISION study participants for CBS activity. At month 12, a statistically significant inverse correlation was observed between homocysteine levels and CBS activity (Spearman's r = -0.58, P<0.0001) after treatment with givosiran.[19]

Four patients with elevated homocysteine levels started a daily multivitamin containing 3 mg of vitamin B6 as pyridoxine during the ENVISION study. Patients received vitamin B6 supplementation between 32 to 34 months. Plasma homocysteine levels prior to and following administration of vitamin B6 are presented in **Table 2.** An increase in CBS activity was observed from months 24 to 36 following vitamin B6 supplementation.[19]

Table 2. Plasma Homocysteine Concentrations (µM) in Four Patients in the ENVISION Study.[20]

	Visit				
Patient/Treatment Arm[a]	**Baseline**	**Month 6**	**Month 12**	**Month 24**	**Month 36**
Patient 1 Placebo	30.2	23.9	241.0	320.9	30.0
Patient 2 Placebo	21.7	26.2	372.2	356.4	96.4
Patient 3 Placebo	20.6	15.1	> 400.0	331.9	46.9
Patient 4 Givosiran	16.0	41.7	45.5	49.9	18.8

[a]Patients in the placebo arm began givosiran treatment at month 6. Both the baseline and month 6 homocysteine measurements were taken from plasma samples collected prior to dosing.

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns related to increases in blood homocysteine. None of the identified cases demonstrated an association of elevations in homocysteine with other AEs, such as thromboembolic events. The risk of clinical consequences of increased blood homocysteine levels is closely monitored through routine pharmacovigilance activities.[21]

ABBREVIATIONS

AE = adverse event; AHP = acute hepatic porphyria; ALA = γ-aminolevulinic acid; CBS = cystathionine-β-synthetase; CKD = chronic kidney disease; DB = double-blind; MTHFR = methylenetetrahydrofolate reductase; OLE = open-label extension; PBG = porphobilinogen; SAE = serious adverse event.

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