FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

# Deferasirox Assessment and Renal Injury

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# Deferasirox and Renal Injury

- What is the impact of deferasirox use in the context of renal injury/impairment
- Is there an exposure-response relationship between exposure and probability of renal injury

# ↑ Deferasirox exposure with ↓ Renal Function

**WARNING: RENAL FAILURE, HEPATIC FAILURE, AND GASTROINTESTINAL HEMORRHAGE**

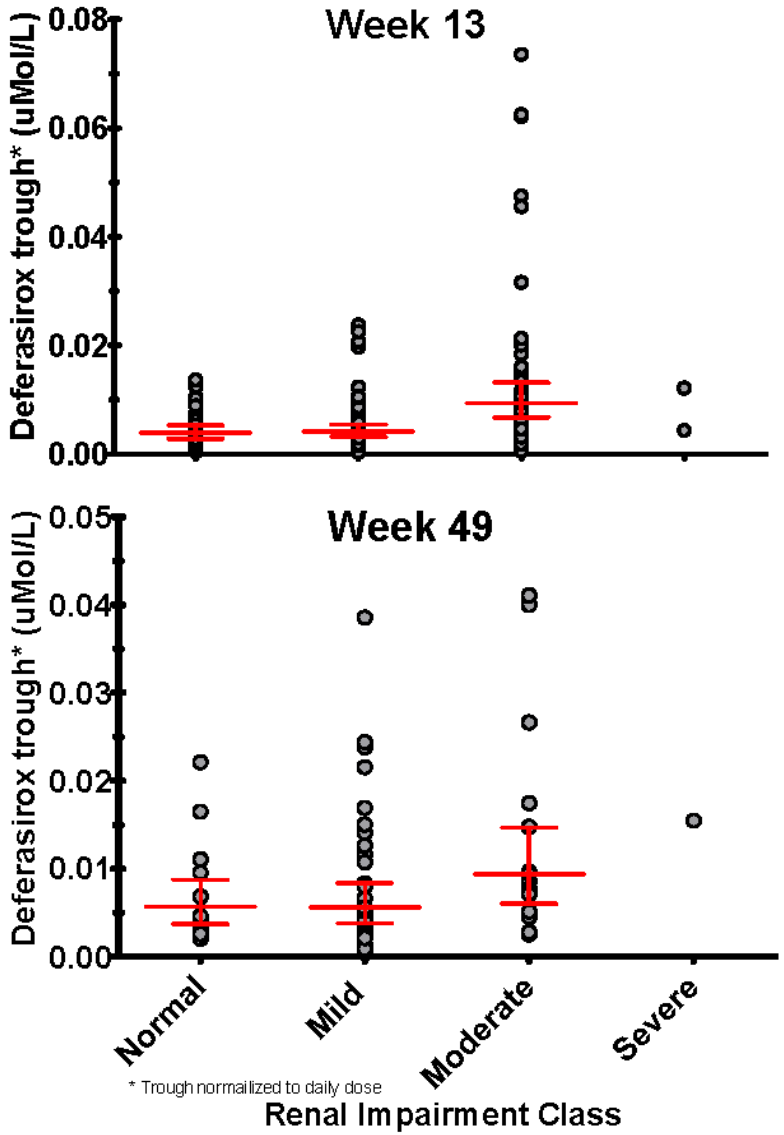
***See full prescribing information for complete boxed warning***

**Exjade may cause:**

- **renal toxicity, including failure (5.1)**
- **hepatic toxicity, including failure (5.2)**
- **gastrointestinal hemorrhage (5.3)**

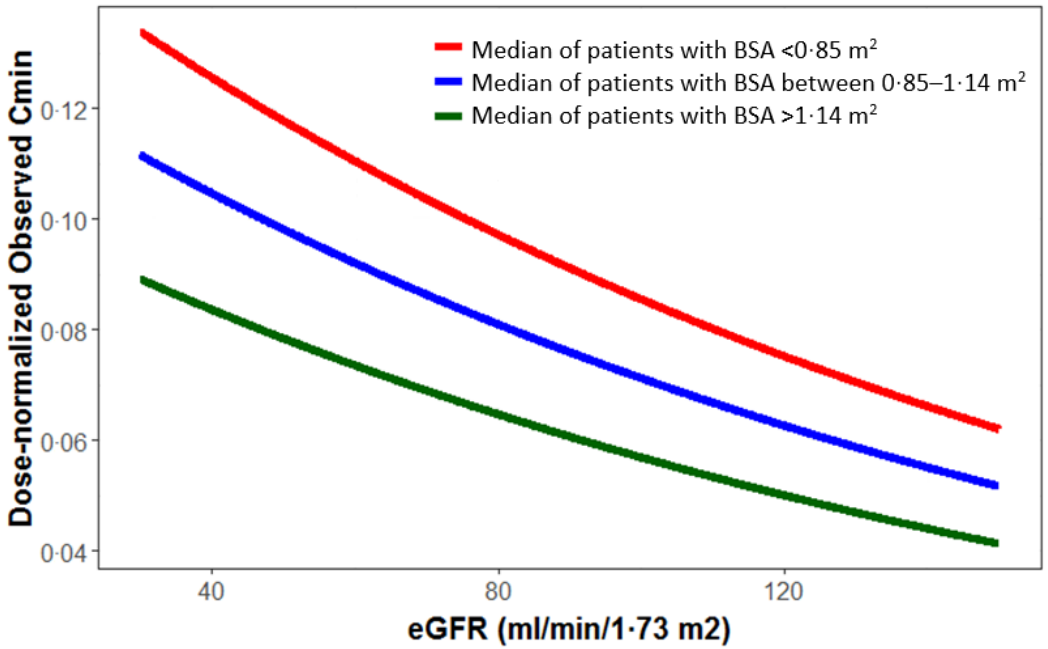
**Exjade therapy requires close patient monitoring, including laboratory tests of renal and hepatic function. (5)**

- increase in dose-normalized trough deferasirox concentrations with declining renal function



# Drug use in the context of ↓ renal function results in ↑ drug exposure

- Relationship between eGFR and drug exposure were evaluated using data obtained from pediatric patients[1]
- Low eGFR was associated with higher dose-normalized trough concentrations
  - Following a 33% ↓ in eGFR from 120 ml/min/1.73 $m^2$ to 80 ml/min/1.73 $m^2$, a 29% ↑ in Cmin is predicted.



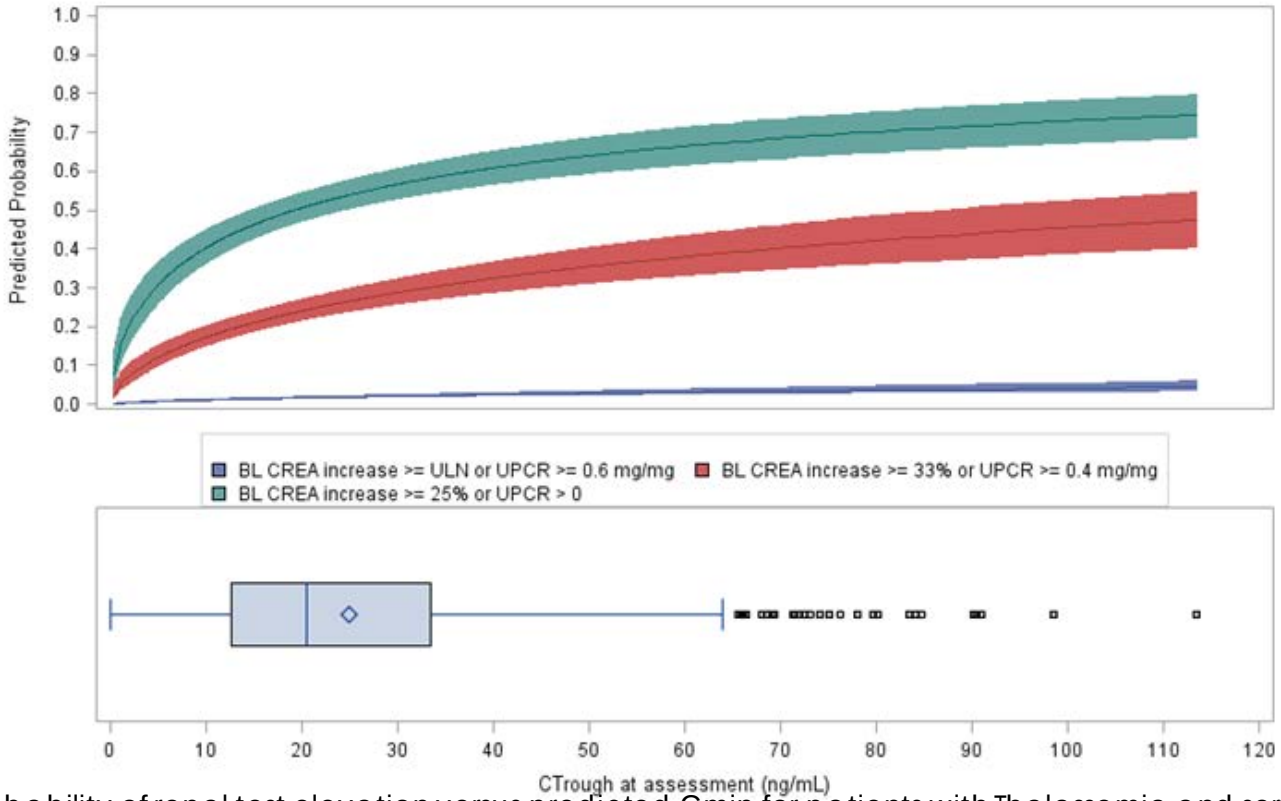

- BSA was a significant covariate indicating that patients with small BSA has higher dose-normalized Cmin than patients with higher BSA



[1] Studies CICL670A2409, CICL670A0107, and CICL670A2201

# ↑ Probability of Renal Injury with ↑ Deferasirox Exposure

- An increase in drug exposure (Cmin) was associated with an increase in risk of renal injury
  - Baseline elevation in serum creatinine, disease type and duration of treatment were found to be statistically significant covariates.




Probability of renal test elevation versus predicted Cmin for patients with Thalassemia and serum creatinine < 1xULN at baseline

- Following a two-fold increase in trough concentration, the estimated probability (odds ratio) (95% CI) of renal injury is 1.52 (1.37, 1.69).

# Summary

- Deferasirox can cause renal injury
- Decreases in renal function can lead to increases in deferasirox concentrations
- Higher deferasirox concentrations increases the probability of renal injury