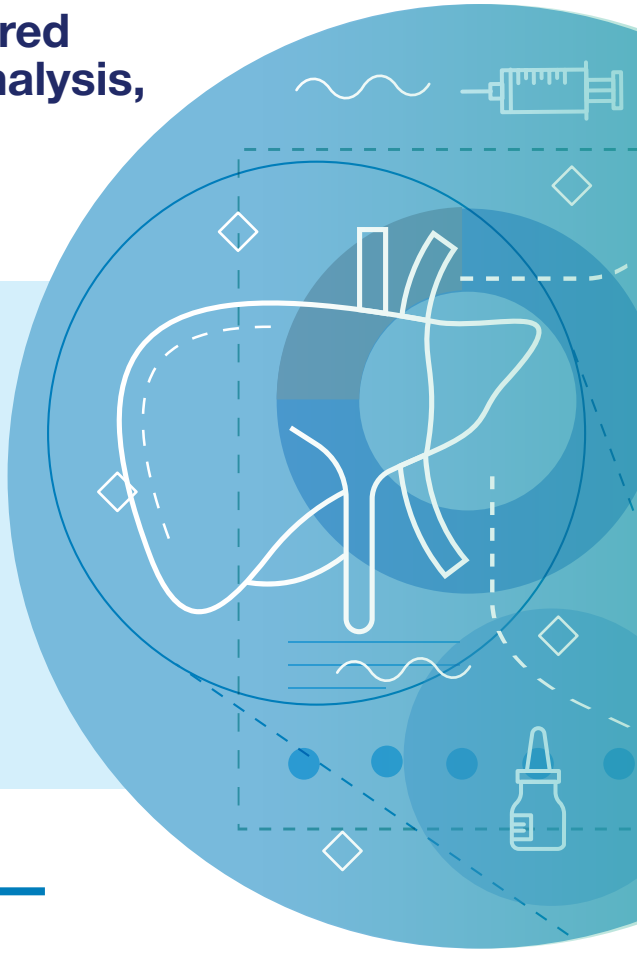
Guidance Snapshot

Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosage

Draft Guidance for Industry



What is covered in this guidance and why is it important?

This guidance provides recommendations for characterizing the impact of hepatic impairment (HI) on the pharmacokinetics and, where appropriate, on the pharmacodynamics of a drug during drug development. This is important to help determine if risk mitigation is needed with the use of the drug in patients with HI.

Considerations for Deciding Whether to Conduct a Dedicated Pharmacokinetic Study in Patients with HI

When a Dedicated Pharmacokinetic Study Should be Conducted:

- Hepatic metabolism and/or excretion accounts for >30 percent of the elimination of absorbed parent drug or active metabolites.
- Minimal drug concentration changes may lead to clinically significant differences in safety or effectiveness.
- The elimination pathways of the drug are not adequately characterized.
- The drug is intended to treat patients with liver disease.
- The drug is likely to be used in patients with HI.

When a Dedicated Pharmacokinetic Study May Not Be Warranted:

If HI is not likely to alter the pharmacokinetics of a drug sufficiently to necessitate a different recommended dosage in patients with HI, a dedicated pharmacokinetic HI study is generally not warranted, unless clinical concerns suggest otherwise.

Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about pharmacokinetics in patients with impaired hepatic function, read the draft guidance. To see additional Guidance Snapshots, check out the pilot program.

Pharmacokinetic Study Design Considerations in Patients with HI

Assessment of Hepatic Function

Hepatic function is assessed using Child-Pugh (CP) criteria or score for cirrhosis and National Cancer Institute (NCI) Criteria for cancer, except hepatobiliary cancers, where CP is recommended. FDA does not recommend NCI Criteria for non-cancer patients. Alternative systems require consultation. Other classification systems can supplement, but not replace CP.

Dedicated Pharmacokinetic Study Design

Sponsors should study mild, moderate, and severe HI with controls. Severe HI alone may be reasonable; significant effects warrant study of other HI groups. Subjects should be clinically stable and exclude acute liver disease. Sample size should support precise pharmacokinetic estimates. A single-dose study with adequate pharmacokinetic sampling is generally sufficient.

Population Pharmacokinetic Approach

If clinical trials adequately represent varying HI and include sufficient concentration data, population pharmacokinetics may characterize HI effects on exposure. Otherwise, a dedicated HI pharmacokinetic study can be conducted. Key elements include adequate subjects, hepatic function assessment, pharmacokinetic sampling, unbound drug and active metabolite measurements, and exposure-response analyses.

Considerations for Pharmacodynamic Assessments

Pharmacodynamic assessments should be included in HI studies where HI could result in pharmacodynamic changes independent of pharmacokinetic changes. Pharmacokinetic and pharmacodynamic data could determine if a different dosage is needed.

DEVELOPMENT OF DOSAGE RECOMMENDATIONS

Dosage recommendations in patients with HI should be based on the overall understanding of the relationship between hepatic function, drug exposure, and the exposure-response relationships for efficacy and safety.

When there is a need for different recommended dosage in patients with HI, the dosage recommendations should be based on exposure-matching to a reference group with an acceptable benefit-risk profile, often the normal hepatic function group.



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LABELING CONSIDERATIONS

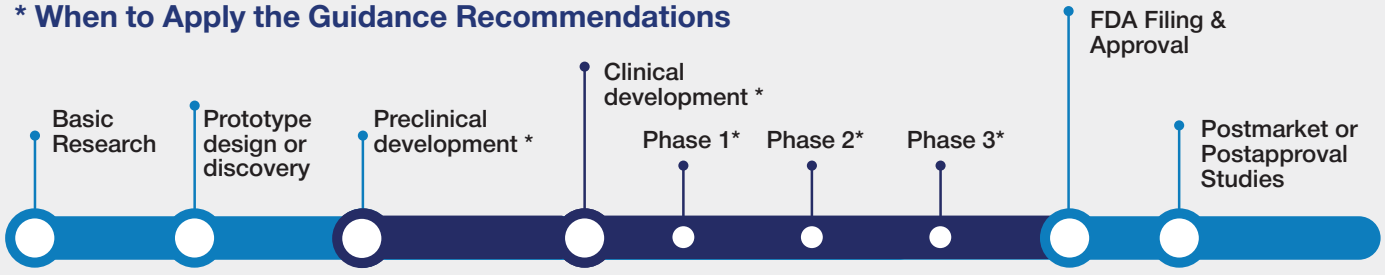
The Prescribing Information should include, as appropriate, essential scientific information needed for the safe and effective use of the drug in patients with HI, including:

- **Pharmacokinetics and pharmacodynamics in patients with HI**
- **Information on hepatic elimination of the drug and relevant active metabolites**
- **Clinical effects of the pharmacokinetic or pharmacodynamic changes in patients with HI**
- **Recommendations to prevent, mitigate, monitor for, or manage risks in patients with HI (e.g., different dosage or monitoring recommendations)**

Drug Development Timeline When to Apply the Guidance Recommendations?

Drug Development Time

*** When to Apply the Guidance Recommendations**



Recommendations From the guidance typically apply during clinical development.
Characterizing the impact of HI on pharmacokinetics during early clinical drug development and employing modeling and simulation strategies, where feasible, can facilitate inclusion of patients with HI in clinical trials.

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