Exploring the Impact of Hepatic Impairment on the Pharmacokinetics of New Molecular Entities: A Comprehensive Analysis of Labeling Information

Yasmeen Abouelhassan[a], Shruti R. Patel[a], and Islam R. Younis[a]
[a] Department of Quantitative Pharmacology and Pharmacometrics, Merck & Co., Inc., Rahway, NJ, USA

Background

- Hepatic impairment (HI) has the potential to alter drug disposition, and therefore is often investigated during drug development to provide appropriate dosing regimen.
- Different approaches have been utilized to inform dosing in patients with HI:
  - Dedicated pharmacokinetic (PK) studies in participants with HI
  - Population PK analysis (popPK)
  - Prediction based on the extent of metabolism or route of administration.

Objectives

- Analyze HI labeling information of FDA-approved small molecules new molecular entities (NMEs) available upon approval.
- Characterize the current approaches used to inform dosing in patients with HI and the type of dosing recommendations.

Methods: FDA-approved NMEs between 2014 and 2023 were evaluated (n=323)

Presence of HI labeling language
Y/N

Type of data to inform labeling
HI study, popPK, etc.

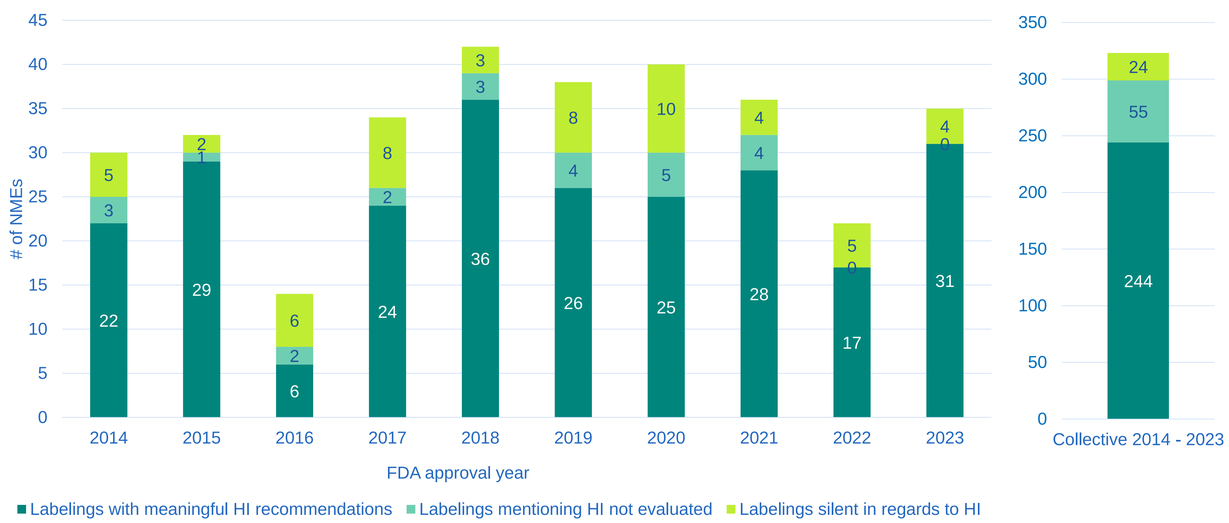
Dosing recommendations
Dose adjustment, not recommended, etc.

Labeling presents data of exposure changes
Y/N

Updates of recommendation
HI information in updated labeling

Results

Figure 1: Number of FDA-approved NMEs with hepatic impairment language in the labeling between 2014 and 2023



Results (continued)

Figure 2: Source to inform HI language in the labeling

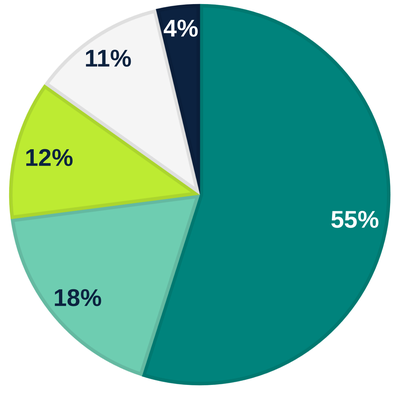


Figure 3: Percent of labelings with HI dosing recommendations according to HI category

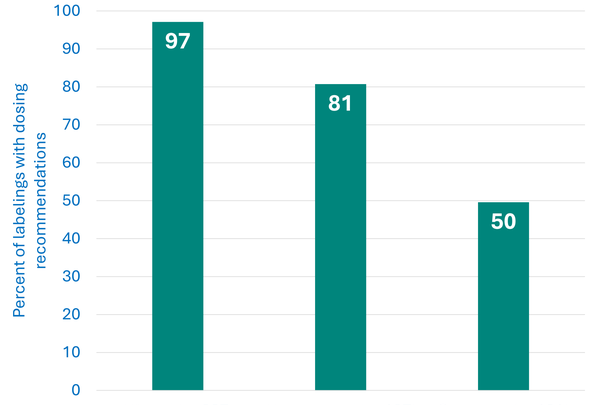
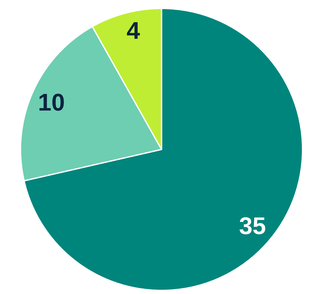


Table 1: Distribution of HI dosing recommendations amongst 128 labelings (data presented as %)

Dosing recommendations	Mild HI	Moderate HI	Severe HI
No dose adjustment (NDA)	82	47	16
Dose adjustment[a]	2	11	9
Monitor	0	0	0
Contraindication	1	2	3
Not recommended (NR)	0	5	7
Not studied (NS)	2	19	34
Combination[b]	8	11	28
NDA + others	4	3	2
NS + NR	1	3	20
Other	4	4	3

[a] Labeling refers to a required or suggested dose adjustment. [b] combination of two or more dosing recommendations.

48 labelings were updated



Conclusions

- At the time of drug approval, the majority of NMEs provided dosing guidance for patients with HI; however, these recommendations were primarily available for mild HI and often suggested no dose adjustment.
- Gaps still exist in informing dosing recommendations for patients with moderate and severe HI.
- Phase 1 PK studies in patients with HI, popPK modeling, and prediction were the primary sources to inform dosing recommendations.
- PBPK had minimal contribution in informing the labeling (used in three cases in combination with another source to inform HI dosing).