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

Renal Dosing in Pediatric Patients: Labeling Considerations

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Disclaimer

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The Ultimate Goal

- To identify safe and effective dosing recommendations for pediatric patients with varying degrees of renal impairment
  - By providing clear and actionable recommendations to healthcare providers in labeling
  - Especially, for drugs with specific dosing recommendations available for adult patients with renal impairment

Adult

eCLcr	Dose	Frequency
> 50 mL/min	2.5 g	Every 8 hours
31 to 50 mL/min	1.25 g	Every 8 hours
16 to 30 mL/min	0.94 g	Every 12 hours
6 to 15 mL/min	0.94 g	Every 24 hours

Pediatrics

?

Modified from ceftazidime/avibactam US prescribing information

Renal Dosing in Pediatric Patients

Current Status

- Not available in FDA-approved labels of most drugs
  - Al-Khouja et al (J Clin Pharmacol. 2020)
    - The study identified 126 drugs with specific recommendations for pediatric patients with renal impairment in major pediatric dosing handbooks
    - Only 15% of FDA-approved labels (19 of 126) had specific pediatric renal dosing recommendations

Challenges and Considerations for Labeling

Lack of data in pediatrics with renal impairment

- Lack of PK, safety, and efficacy data in pediatric patients with renal impairment
  - Rarity of the condition
  - Exclusion of patients with any degree of renal impairment in pediatric clinical trials

Example

Population	Exclusion Criteria in Registrational Clinical Trials	Approved Renal Dosing
Adult	**eCLcr < 50 or 60 mL/min** as calculated by the Cockcroft-Gault (C-G) equation	**Approval:** No dosage adjustment is required for patients with mild or moderate RI (eGFR > 30 mL/min/1.73 m^2)
Pediatrics	**eGFR < 90 mL/min/1.73m^2**, as calculated by the Schwartz formula	Not specified

Challenges and Considerations for Labeling

Understanding the Basis of Adult Renal Dosing

- Basis for dosing recommendations in adults with renal impairment
  - Exposure-matching approach
    - E.g., 2-fold higher exposures in adult patients with severe renal impairment as compared to those with normal renal function → a 50% dose reduction in the population
  - Threshold approach
    - E.g., No dose adjustment is recommended in patients with severe renal impairment or end-stage renal disease, as available safety data support the use of the full dose despite higher drug exposures.

- Key points for consideration when translating adult renal dosing to pediatrics
  - Translating adult renal impairment PK data (different equations estimating eGFR or eCLcr; BSA indexing; renal function maturation)
  - Extrapolation of safety and efficacy from adults to pediatrics

Labeling Examples #1

General guidance

- Outlining a general principle without specific dosing recommendations
  - Triumeq and Triumeq PD are not recommended in patients with creatinine clearance less than 30 mL/min and pediatric patients with a similar degree of renal impairment based on age-appropriate assessment of renal function.
  - Although the pharmacokinetics of fluconazole has not been studied in children with renal insufficiency, dosage reduction in children with renal insufficiency should parallel that recommended for adults.
  - Although there are insufficient data to recommend a specific dose adjustment of lamivudine in pediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval should be considered.

Triumeq, Diflucan, Epivir US prescribing information

Labeling Examples #2

Recommendations for Adults ≈ Recommendations for Pediatrics

Drug	Recommendation	Adult	Pediatrics
Ceftazidime/Avibactam	50% dose reduction	estimated **CLcr of 31 to 50 mL/min (Cockcroft-Gault)**	Pediatric patients (2 years and older) with eGFR of **31 to 50 mL/min/1.73m2** (**Schwartz bedside formula)**
Lacosamide	25% reduction of the maximum dosage	**Severe renal impairment (Cockcroft-Gault)**	Pediatric patients with CLcr less than **30 mL/min/1.73m2 (Schwartz equation)**
Sacubitril/Valsartan	50% reduction of the usually recommended starting dose	Severe renal impairment **(eGFR < 30 mL/min/1.73 m2)**	Severe renal impairment **(eGFR < 30 mL/min/1.73 m2)**

Labeling Examples #3

Recommendations for Adults ≠ Recommendations for Pediatrics

- **Valganciclovir**

Adults

VALCYTE 450 mg Tablets		
CrCl* (mL/min)	**Induction Dose**	**Maintenance/ Prevention Dose**
≥ 60	900 mg twice daily	900 mg once daily
40 – 59	450 mg twice daily	450 mg once daily
25 – 39	450 mg once daily	450 mg every 2 days
10 – 24	450 mg every 2 days	450 mg twice weekly
< 10 (on hemodialysis)	not recommended	not recommended

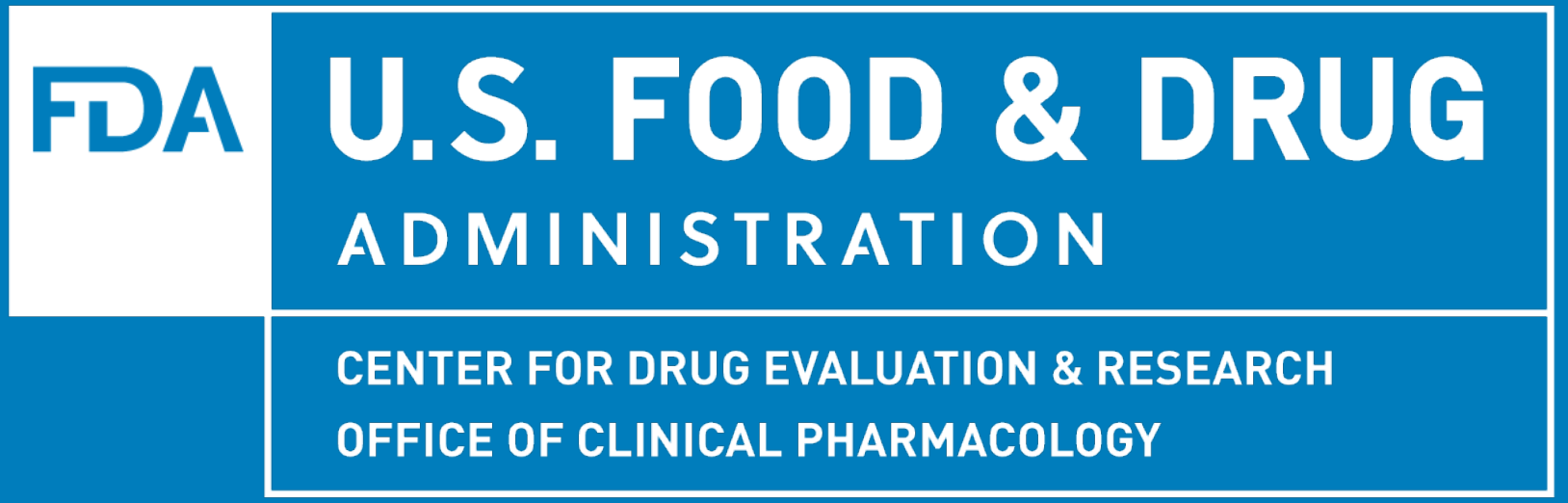
Pediatrics

Pediatric Dose (mg) = 7 X Body Surface Area X Creatinine Clearance derived from a modified Schwartz formula

- **Dabigatran**
  - Adults: 120 mg orally twice daily for <u>CrCL > 30 mL/min</u>
  - Pediatrics: weight-based dosing for patients <u>**with eGFR > 50 mL/min/1.73m2**</u>. Due to lack of data and the risk of increased exposure, avoid use of dabigatran in pediatric patients with eGFR < 50 mL/min/1.73m2

Summary

- Compared to adult patients with renal impairment, dosing regimens for pediatric patients with renal impairment are often not readily available for most drugs.
- This is likely due to multiple challenging aspects involved in generating appropriate dosing recommendations for this population.
- Further discussion is needed to establish improved labeling recommendations for pediatric patients with renal impairment.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