Development of Antihypertensive Therapies for Use in Pediatric Patients Workshop
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Landscape of Drug Development for Management of Pediatric Hypertension

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Disclosures

- I have no financial relationships to disclose relating to this presentation
- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

How Drugs are Typically Developed for Use in Children with Hypertension*

Drugs are usually first developed for use in adults with hypertension

- If meet certain criteria (new active ingredient, indication, dosage form, dosing regimen, or route of administration), FDA has the authority to require an assessment of the safety and effectiveness of the product for the claimed indication in children
  - Under the 2003 Pediatric Research Equity Act (PREA)
  - Does not retroactively mandate studies for previously approved drugs

- FDA could also request voluntary studies for a specific drug for one or more indications under a “Written Request” if it determined that use of a drug in children may produce health benefits in children
  - Under 1997 Food and Drug Modernization Act (FDAMA), later 2002 Best Pharmaceuticals for Children Act (BPCA)
  - Could grant 6 months marketing exclusivity to sponsor that completed pediatric studies

* Unless otherwise stated, "children" or "child" refers to the entire pediatric age range in this presentation

Number of Orally Administered Drugs Approved for the Treatment of Hypertension in Adult and Pediatric Patients

To date, excluding fixed combination drug products, there are 61 drugs approved for the treatment of hypertension in adults and 16 in pediatric patients.

Drug Class	Adult	Pediatric
ACE Inhibitors	10	5
Diuretics (Thiazide, Loop & Potassium-sparing)	10	2
Beta-Blockers	9	1
Angiotensin II Receptor Blockers (ARBs)	8	4
Calcium Channel Blockers	8	1
Centrally-Acting Agents	4	0
Alpha-1 Blockers	3	0

Drug Class	Adult	Pediatric
Alpha-Beta Blockers	2	0
Aldosterone Antagonists / MRAs	2	0
Direct Vasodilators	2	2
Direct Renin Inhibitor	1	1
Endothelin Receptor Antagonist	1	0
Aldosterone Synthase Inhibitor	1	0
TOTAL	**61**	**16**

First approval: hydralazine in 1953

ACE, angiotensin converting enzyme

Pediatric Antihypertensive Drug Approvals

- Of the 16 drugs approved to date
  - 9 (56%) are approved for patients 6 years of age and older
    - 4 ACEi, 2 ARBs, 1 beta blocker, 1 calcium channel blocker, 1 renin inhibitor
  - 3 (19%) are approved for patients <6 years of age
    - Enalapril for 1 month of age and older (approved in 2002)
    - Candesartan for 1 year of age and older (2009)
    - Valsartan for 6 years of age and older (2007; expanded down to 1 year of age in 2021)
  - 4 (25%) are older drugs with pediatric dosing information for hypertension
    - Hydralazine, chlorothiazide and hydrochlorothiazide were approved for the treatment of hypertension in adults in the 1950s
      - Pediatric dosing information was added based on anecdotal/empirical information in the 1960s and 1970s
      - Hydralazine: pediatric age not specified; chlorothiazide and hydrochlorothiazide: down to birth
    - Minoxidil approved for the treatment of hypertension in 1979
      - Pediatric dosing information for all age groups with statement that dosing recommendations “can be considered only a rough guide at present and a careful titration is essential”

Typical Study Designs That Have Supported Pediatric Antihypertensive Drug Approvals

- Single or multiple dose pharmacokinetics (PK) study

  Together with

- A randomized withdrawal study design (commonest design)
  - Typically includes an initial dose ranging phase that evaluates 3 dose levels (sometimes 2 dose levels) for 2-4 weeks, during which patients are randomized to low, medium, or high dose (or low or high dose if 2 dose levels) of study drug
  - The dose ranging phase is then typically followed by a blinded randomized withdrawal phase of 2 weeks duration, during which patients are randomized to placebo or remain on study drug

  And/Or

- A randomized, placebo-controlled dose ranging study, during which patients are typically randomized to one of three dose levels of study drug or placebo for ~4 weeks (less common design)

The Evidentiary Standard for Pediatric Drug Approval

- Same standard as adults
- Demonstrate substantial evidence of effectiveness for the proposed indication
- Adequate safety information to allow for appropriate risk benefit analysis
- Evidence-based labeling including dosing that adequately guides patients and prescribers on safe and effective use of the drug

Where We are Now

- Pharmaceutical companies are developing new dosage forms (e.g., oral suspension/solution) of old drugs such as ACE inhibitors, ARBs, calcium channel blockers, and beta blockers for the treatment of hypertension
  - Can rely on FDA's finding of efficacy and safety of the "reference" drug for the proposed indication(s) and may not need to conduct additional clinical studies other than a bioequivalence study to bridge to the "reference" drug
  - The new dosage form provides FDA the authority under PREA to require studies to obtain data to label these products for use in pediatric patients <6 years of age or the unindicated pediatric population
  - Raises questions of what data are needed from the pediatric study(ies), how these data can be efficiently and feasibly obtained, and whether data from adequate and well controlled study(ies) in adults/approved population with hypertension that were used to demonstrate effectiveness and safety could be leveraged to support the pediatric study(ies)
  - Given widespread off-label use of these drugs for the treatment of hypertension, it is unclear what study designs are feasible

Goals for Day 1 of the Workshop

- Understand the degree to which scientific data support extrapolation of efficacy from adults to older pediatric patients with chronic systemic hypertension, and from older to younger pediatric patients with chronic systemic hypertension
- Discuss what data could be leveraged from off-label use of drugs for the treatment of hypertension and what data would be needed from the pediatric study to support use in that population
- Discuss what study designs/study design elements might be feasible to obtain the data needed to provide dosing recommendations for safe and effective use of drugs, particularly in children <6 years of age

Where We are Now: Day 2 of the Workshop

- Products are also being developed for lowering blood pressure in adults who are not adequately controlled on other agents

- Day 2 of the Workshop will focus on
  - Understanding the unmet need in pediatric patients with hypertension who are not adequately controlled on other agents
  - Understanding the degree to which scientific data support extrapolation of efficacy from adults to pediatric patients with hypertension that is not adequately controlled on other agents, and down to what age

Thank you for listening and for your participation!

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Back Up

Pediatric Drug Approvals for Hypertension

Drug Class	Proprietary Name	Active Ingredient	Dosage Form	Adult Approval	Pediatric Approval	Pediatric Age group	PREA	WR
ACEi	Vasotec	Enalapril maleate	Oral Tablet	1985	2001	≥1 month	NA	Oct-1998
	Prinivil	Lisinopril	Oral Tablet	1987	2003	≥6 years	NA	Nov-1999
	Zestril	Lisinopril	Oral Tablet	1988	2003	≥6 years	NA	Dec-1998
	Monopril	Fosinopril sodium	Oral Tablet	1991	2003	≥6 years	NA	Jan-2003
	Losentin	Benazepril HCl	Oral Tablet	1991	2004	≥6 years	NA	Jul-2003
ARBs	Cozaar	Losartan potassium	Oral Tablet	1995	2004	≥6 years	NA	Mar-2002
	Actand	Candesartan cilexetil	Oral Tablet	1998	2009	≥1 year	NA	Mar-1999
	Diovan	Valsartan	Oral Tablet	2001	2007	≥1 year	NA	Dec-2000
	Benicar	Olmesartan medoxomil	Oral Tablet	2002	2010	≥6 years	NA	Mar-2001
Diuretics	Diuril	Chlorothiazide	Oral Tablet	1958	Empiric pediatric dosing added 1960s/1970s	All ages	NA	NA
	Hydrodiuril	Hydrochlorothiazide	Oral Tablet	1959	Empiric pediatric dosing added 1960s/1970s	All ages	NA	NA
Vasodilators	Apresoline	Hydralazine hydrochloride	Oral Tablet	1953	Empiric pediatric dosing added 1960s/1970s	Not specified	NA	NA
	Loniten	Minoxidil	Oral Tablet	1979	1979	All ages	NA	NA
Beta blockers	Toprol-XL	Metoprolol succinate	Oral Tablet	1992	2007	≥6 years	NA	Apr-2003
CCB	Norvasc	Amlodipine besylate	Oral Tablet	1992	2004	≥6 years	NA	Nov-2001
Renin Inhibitor	Tekturna	Aliskiren	Oral Tablet/pellets	2007	2017	≥6 years and ≥50 kg	Y	May-2008

Basis for Pediatric Antihypertensive Drugs Approvals (1 of 3)

Active Ingredient	Approved Ages	Pediatric Studies
Enalapril maleate	1m – 16 years	• PK study, age 2m-16 years (n=40) • Double-blind, randomized dose ranging study, age 6-16 years (n=110)
Lisinopril	6 – 16 years	• PK study (n=29) • Dose-response (2-week), double-blind, randomized withdrawal study (n=115)
Fosinopril sodium	6 – 16 years	• PK study (n=20) • Dose-response (4-week), double-blind, randomized withdrawal study (n=252)
Benazepril HCl	6 – 16 years	• PK study (n=45) • 4-week dose titration (3 dose levels), 2-week randomized withdrawal study (n=107)
Losartan potassium	6 – 16 years	• PK study (n=25) • Dose-response (3-week, 3 dose levels), double-blind, randomized withdrawal study (n=177)
Candesartan cilexetil	1 – 16 years	• Dose-ranging (3 dose levels), age 1 to <6 years (n=93) • 4-week dose-ranging, randomized, double-blind, placebo-controlled (randomized to one of 3 dose levels or placebo), age 6 to <17 years (n=240)

Basis for Pediatric Antihypertensive Drugs Approvals (2 of 3)

Active Ingredient	Approved Ages	Pediatric Studies

Valsartan	1 – 16 years	• PK study, age 1-16 years (n=26)
		• Dose-response (3 dose levels), double-blind, randomized withdrawal study, age 6-16 years (n=261)
		• 3 randomized, double-blind, dose ranging studies age 1 to <6 years, starting with a placebo run-in period of 4 -28 days, followed by
		  • 2-week double-blind dose ranging (3 dose levels), followed by 2-week double-blind, randomized withdrawal phase (n=90)
		  • 6-week randomized, double-blind dose-ranging (3 dose levels) followed by 2-week double-blind, randomized withdrawal phase (n=75)
		  • 6-week randomized, double-blind dose-ranging (2 dose levels) then 20-week open-label phase when all received valsartan and were titrated up at fixed increments and at fixed intervals if SBP was ≥90th percentile (to maximum of 4 mg/kg) (n=127)

Olmesartan medoxomil	6 – 16 years	One study ages 1 to 16 years (n=361) • 2-week dose ranging (2 dose levels), 2-week randomized, double-blind, withdrawal study, age 6-16 years (n=302) • 3-week open-label phase during which all received the same weight-based dose (0.3 mg/kg), then 2-week double-blind randomized withdrawal phase, age 1-5 years and ≥5 kg (n=59)

Basis for Pediatric Antihypertensive Drugs Approvals (3 of 3)

Active Ingredient	Approved Ages	Pediatric Studies
Metoprolol succinate	≥6 years	• PK study (n=120) • 4-week randomized, double-blind, placebo-controlled, dose ranging study, age 1 to <6 years (n=144)
Amlodipine besylate	6 – 17 years	• PK study (n=62) • 4-week dose ranging (2 dose levels), 4-week randomized, double-blind, withdrawal study (n=268)
Aliskiren	6 – 16 years	• PK study (n=39) • 4-week dose-response (3 dose levels), 4-week randomized withdrawal study (n=267)