CLINICAL REVIEW

Application Type	NDA
Submission Number	21-437 S005
Submission Code	SE5
Letter Date	07/31/07
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Reviewer Name	Thomas A. Marciniak, M.D.
Review Completion Date	01/16/08
Established Name	eplerenone
(Proposed) Trade Name	Inspra
Therapeutic Class	aldosterone receptor antagonist
Applicant	Merck
Priority Designation	P
Formulation	tablets
Dosing Regimen	once to twice daily
Indication	hypertension
Intended Population	children aged 6-16

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I do not recommend approval of eplerenone for the treatment of hypertension in children. The pediatric efficacy study failed on its primary endpoint and its secondary endpoints do not provide evidence of efficacy of eplerenone in treating hypertension in children. The results of the one-year safety study suggest that eplerenone in children exhibits the same adverse effects as seen in adults, including increases in potassium and creatinine. Eplerenone also causes sex-hormone related adverse effects such as gynecomastia. Whether eplerenone has other safety concerns in children, such as reduction in serum calcium and effects upon growth, is less clear.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Because I do not recommend approval, I do not recommend any post-marketing risk management activities.

1.2.2 Required Phase 4 Commitments

Because I do not recommend approval, I do not recommend any required phase 4 commitments.

1.2.3 Other Phase 4 Requests

Because I do not recommend approval, I do not recommend any other phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Eplerenone (Inspra) is an oral aldosterone receptor blocker (similar to spironolactone) approved for the treatment of hypertension in adults in 2002. This supplement reports pharmacokinetic (PK) and clinical safety and efficacy studies in hypertensive children done in response to a pediatric written request. The studies reported are two pharmacokinetic studies, the pivotal double-blind, dose-ranging efficacy study with placebo-controlled withdrawal, and an open-label one-year safety study.

1.3.2 Efficacy

The pivotal efficacy study, Study A6141001, was a randomized, double-blind, 6-week, dose-response study with a blinded 4-week placebo-withdrawal phase. In the first phase, 304 children 6-16 with seated SBP greater than or equal to the 95th percentile for age, gender, and height were randomized (1:1:3 ratio) to receive one of three doses of eplerenone (25 mg QD, 25 mg BID, or 50 mg BID) and, in the second phase, subjects underwent a placebo-controlled randomized withdrawal phase, where half of the subjects continued active treatment, and half received placebo. Children who were uncontrolled on other antihypertensives were allowed to enroll and continue their prior medication. Study enrollment was closed after 304 subjects were randomized because recalculation of power based on estimates of blood pressure variability from the long term safety study.

The primary efficacy endpoint was change in SBP from baseline of the second phase to the end-of-study visit, with an ordered evaluation from high dose to low dose. The sponsor's analysis of this endpoint for the high dose (50 mg BID) yielded a least squares mean difference from placebo of -2.8 mm Hg and a p-value of 0.0484. However, the sponsor's analysis excluded one patient treated in the second phase but without post-treatment BP measurements. For the pre-specified analysis, i.e., including all patients treated and performing LOCF, the p-value is 0.0664, not significant. While the sponsor excluded only one patient and that patient's exclusion is consistent with the analysis set pre-specified for many antihypertensive trials (the so-called "modified intention-to-treat" consisting of all treated patients who have at least one post-treatment BP measurement), the suggestion of a beneficial effect of eplerenone in children with hypertension is marginal and not robust: The mean changes in BP among the various treatment groups in both phases appear randomly distributed and the p-values support that they are largely random. I judge that this study does not provide substantial evidence of antihypertensive efficacy of eplerenone in children.

1.3.3 Safety

The long-term safety study, Study A6141077, had entry criteria similar to the efficacy study and, in fact, 71 of the 150 patients enrolled into the safety study from the efficacy study. One patient enrolled in the study but withdrew prior to taking study medication and was not included in any safety evaluations. Therefore, the safety population comprised 149 patients at the start. Twenty (13%) patients withdrew and 106 patients completed at least one year of treatment. The general design of this open-label safety study was simple: A six-week dose adjustment phase followed by chronic treatment to for at least one year. Potassium sparing diuretics, potassium supplements, and strong CYP3A4 inhibitors were prohibited, but "standard of care" otherwise was allowed. While eplerenone was to be titrated to 50 mg BID and could also be down-titrated, the protocol did not provide instructions on how to titrate other antihypertensives. About 46% of the patients took other antihypertensives, most commonly enalapril or amlodipine as for the efficacy study.

Eplerenone in children largely causes the same types of adverse events as those seen in adults. Increases in serum potassium and creatinine were dose-related and of particular concern in patients with reduced renal function. Eplerenone also produced sex-hormone related AEs such as one case of gynecomastia in a 15-year-old boy. Whether these sex-hormone effects can lead to problems with sexual development is beyond the scope of a one-year study.

1.3.4 Dosing Regimen and Administration

The dosing regimen used for children was that approved for adults. The sponsor did not develop a new formulation for young children unable to swallow tablets. The efficacy study was too small to explore variations in dosing regimen.

1.3.5 Drug-Drug Interactions

Drug-drug interactions were not studied in this submission

1.3.6 Special Populations

This submission is a pediatric submission in response to a Written Request.

Abbreviations

ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ABPM	ambulatory blood pressure monitoring
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
AST	aspartate aminotransferases (SGOT)
AUC	area under the curve
BID	twice a day
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
DBP	diastolic blood pressure
DSI	Division of Scientific Investigation (FDA)
ECG	electrocardiogram
EEG	electroencephalogram
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GFR	glomerular filtration rate
GI	gastrointestinal
GLP	Good Laboratory Practices
GRA	glucocorticoid remediable aldosteronism
HCTZ	hydrochlorothiazide
HF	heart failure
ICH	International Conference on Harmonization
IRB	institutional review board
ISE	Integrated Summary (Review) of Efficacy
ISS	Integrated Summary (Review) of Safety
ITT	intention-to-treat
IVRS	interactive voice response system
LDH	lactate dehydrogenase
LOCF	last observation carried forward
LSM	least squares mean
MSDBP	mean seated diastolic blood pressure
MSSBP	mean seated systolic blood pressure
NDA	New Drug Application
NOS	not otherwise specified

NS	not significant
OD	once a day
PD	pharmacodynamic(s)
PEY	person-exposure-year
PK	pharmacokinetic(s)
PRA	plasma renin activity
PRC	plasma renin concentration
QD	once daily
QTc	QT interval corrected (for heart rate)
RAAS	renin-angiotensin-aldosterone system
RBC	red blood cells
SAE	serious adverse event
SAS	Statistical Analysis System
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
ULN	upper limit of normal
US	United States
WR	Written Request (for pediatric studies)

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Eplerenone (Inspra) is an oral aldosterone receptor blocker (similar to spironolactone) approved for the treatment of hypertension in adults in 2002. This supplement reports pharmacokinetic (PK) and clinical safety and efficacy studies in hypertensive children done in response to a pediatric written request.

2.2 Currently Available Treatment for Indications

Treatment of hypertension in children has been more elusive than treatment of hypertension in adults. While most older children may have essential hypertension like their adult counterparts, younger children frequently have secondary hypertension, most commonly related to renal disease. Prior to the Food and Drug Administration Modernization Act (FDAMA) of 1997 most available antihypertensives were use in treating children but none were specifically approved for use in children. Since FDAMA, beta blockers, ACE inhibitors, and angiotensin receptor blockers have been studied in hypertensive children.

2.3 Availability of Proposed Active Ingredient in the United States

Eplerenone has been marketed in the United States since 2002. There have not been any post-marketing safety issues raised regarding it.

2.4 Important Issues with Pharmacologically Related Products

Eplerenone, like the other marketed aldosterone blocker spironolactone, raises serum potassium levels. The increases in potassium can be problematic in patients with reduced renal function and, for eplerenone, in diabetics. Spironolactone also has estrogenic effects, leading to gynecomastia in men and menstrual irregularities in women. Eplerenone may have a lower risk than spironolactone of causing such problems but any hormonal effects would be more problematic in children.

2.5 Presubmission Regulatory Activity

The Division issued a formal written request for pediatric studies to the sponsor on August 17, 2000, and reissued it on July 2, 2002, following the enactment of the Best Pharmaceuticals for Children Act. The Division and the sponsor discussed the written request (WR) at a teleconference on July 21, 2000, and at a meeting on October 25, 2000. The sponsor submitted an efficacy protocol on October 13, 2000, as Serial 195 and a pediatric pharmacokinetic (PK) protocol on May 14, 2001, as Serial 241. The efficacy protocol was for a study in children with glucocorticoid remediable aldosteronism (GRA). The sponsor submitted an outline of a proposed revised pediatric program not restricted to GRA on November 3, 2003, and provided a draft efficacy protocol on December 2, 2003. The Division discussed the pediatric program with the sponsor at a teleconference on December 18, 2003, and a meeting on March 18, 2004. The sponsor submitted a protocol for a long-term safety study on March 23, 2004, as Serial 408, and for an efficacy study in children with hypertension (not limited to GRA) on April 27, 2004, as Serial 410. The Division issued a revised WR on October 1, 2004. The sponsor amended the long-term safety study to be consistent with the revised WR in Serial 441 dated December 28, 2004. The Division issued a final revised WR on June 7, 2006, extending the due date and

relaxing the enrollment of black children from 40-60% to at least 25%. This revised WR dated June 7, 2006, was the last one issued. It specified the following for the pediatric studies:

- At least 50% of subjects were to be prepubertal (eg, ≤12 years of age).
- At least 25% of subjects were to be black.
- The formulation used in the clinical studies was to be well-characterized and suitable for the population under study.
- Pharmacokinetic sampling was to be conducted in subjects spanning the same age range as those studied for effectiveness.
- Studies were to include dose-ranging in pediatric subjects with hypertension, with a design comparable to one of several options outlined in the Written Request, and the results of such a study were to be such that the study was considered interpretable, either having ≥90% power of detecting a 3 mm Hg difference in blood pressure or successfully meeting its primary endpoint.
- Safety evaluation of the use of eplerenone in children was to be derived from the following sources:
    - Safety data from a controlled trial and a 1-year open treatment phase following the trial.
    - Summary of all available information on the safety of eplerenone in hypertensive pediatric patients, including (a) a summary of the published literature, and (b) formal analyses of published and unpublished data.

2.6 Other Relevant Background Information

I know of no other relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The submission does not include changes in chemistry, manufacturing, and control (CMC). The sponsor did not develop a new formulation for young children.

3.2 Animal Pharmacology/Toxicology

The submission does not include new animal pharmacology or toxicology data.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data are the clinical study reports and data provided in the submission.

4.2 Tables of Clinical Studies

I list in Table 1 the clinical studies reported in this submission.

Table 1: Clinical Studies

#	Description	Ages	Dosages	N
NE3-01-02-054	bioavailability of crushed tablet	18-45	100	16
NE3-01-02-055	single-dose PK	2-16/18-65	12.5-100	14/8
A6141001	double-blind dose-ranging followed by placebo-controlled randomized withdrawal	6-16	0/25/50/100	84/58/62/184
A6141077	open-label one-year safety with pop PK	6-16	25-100	150

The FDA clinical pharmacology review discusses the two PK studies (NE3-…) in detail as well as the population PK analysis combining the data from NE3-01-02-055 and A6141077. I discuss primarily the efficacy and the safety studies (A614…).

4.3 Review Strategy

I initially verified that the sponsor's reports of the studies were consistent with the final revised WR. I re-analyzed the SAS data sets to confirm whether the sponsor's efficacy analyses were appropriate and I checked the adverse event, laboratory, and neurocognitive test data for safety signals.

4.4 Data Quality and Integrity

I did not request Division of Scientific Investigations (DSI) audits because enrollments at individual sites were typically low. I reviewed case report forms and the SAS data sets to verify that source documents were consistent with the reports and tabulations.

4.5 Compliance with Good Clinical Practices

The clinical overview states that the studies were conducted in compliance with Good Clinical Practices and in accordance with regional, national and local guidances and regulations governing study conduct in human subjects (Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines), including review by Institutional Review Boards/Ethics Committees, and for obtaining written informed consent from subjects and/or their parents or guardians, and where appropriate, assent from the children.

4.6 Financial Disclosures

There are two covered studies for this supplemental NDA. The submission states that these covered studies were not funded via variable compensation and none of the investigators in the studies hold any form of propriety interest in Inspra. Two of the 207 investigators reported significant payments of other sorts.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Please see the FDA clinical pharmacology review for a detailed review of the PK studies. The following is the sponsor's summary of the most pertinent findings: Based on the population pharmacokinetic analysis of the eplerenone pediatric combined dataset from a single dose, open-label study (NE3-01-02-055) and a multiple-dose safety study (A6141077), the population

estimate for CL/F in pediatric hypertensive subjects was within 19% of the estimates in adult hypertensive subjects (5.95 in pediatric subjects versus 7.33 L/h in adult subjects), indicating that the oral clearance of eplerenone in pediatric hypertensive subjects was not substantially different than that in adult hypertensive subjects. The 95% confidence interval for CL/F (4.83–7.38 L/h) contained the adult population mean value (7.33 L/h). The 19% lower CL/F in pediatric hypertensive subjects predicts an approximately 25% increase in total exposure to eplerenone. The covariate analyses confirmed the results from the population pharmacokinetic analysis of the single-dose pediatric Study NE3-01-02-055, i.e., age and total body weight did not have statistically significant effects on CL/F estimates in the pediatric population. The effect of total body weight on apparent central volume of distribution (V_c/F) was found to be statistically significant. The population mean estimate of V_c/F for a hypertensive pediatric subject weighing 45 kg was 30.7 L. For pediatric hypertensive subjects, the estimated body weight effect was 0.500 L/kg, meaning that their V_c/F was increased or decreased by 0.5 L for every kg of total body weight increase or decrease. As a result, a pediatric subject with a lower total body weight will have a lower volume of distribution and a higher maximum plasma concentration (C_{max}) than a pediatric subject with a higher total body weight.

5.2 Pharmacodynamics

The submission does not include studies of pharmacodynamic parameters other than the effects upon blood pressure discussed in the Integrated Review of Efficacy below.

5.3 Exposure-Response Relationships

The pivotal efficacy study A6141001 included three dosages as well as a placebo-controlled withdrawal. I discuss the available data on exposure-response relationships for the pediatric population in the Integrated Review of Efficacy below. In short the data did not confirm an exposure-response relationship in the pediatric population.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The targeted indication is the treatment of hypertension in children.

6.1.1 Methods

This submission provides one pivotal efficacy study, A6141001. I review that study below.

6.1.2 General Discussion of Endpoints

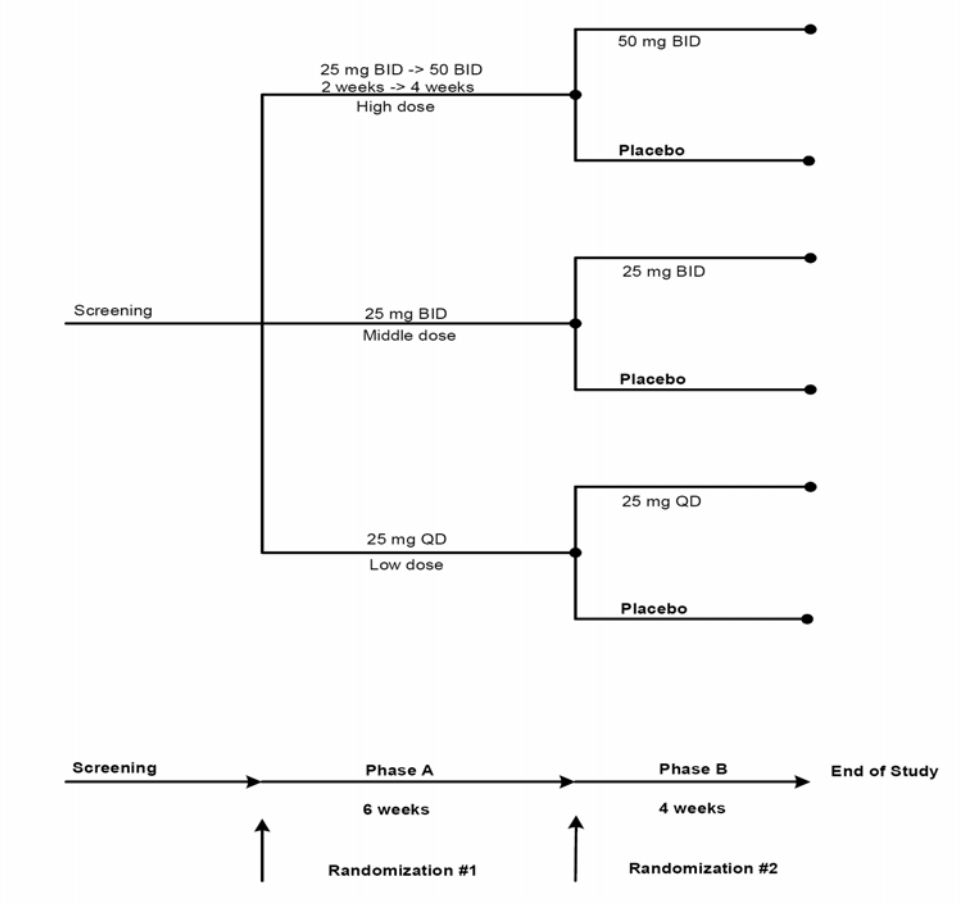
The primary endpoint was seated trough cuff blood pressure (BP), the usual endpoint for studies of antihypertensives. Systolic BP was the primary endpoint while diastolic BP was a secondary endpoint.

6.1.3 Study Design

Study A6141001 was a randomized, double-blind, dose-response study with a blinded placebo-withdrawal phase, to evaluate the efficacy and safety of eplerenone in the treatment of hypertension in children. This study trial design was based on the options described in the WR. The final trial design was a 6-week randomized double-blind dose-response phase (Phase A), followed by a 4-week randomized placebo-withdrawal phase (Phase B). In Phase A, subjects

were randomized (1:1:3 ratio) to receive one of three doses of eplerenone (25 mg QD, 25 mg BID, or 50 mg BID) and, in Phase B, subjects were to undergo a placebo-controlled randomized withdrawal phase, where half of the subjects continued active treatment, and half received placebo, as detailed in Figure 1. The sponsor picked the dosages to cover the range from lower than the approved adult starting dose to higher (on a weight basis) than the approved adult maximum dosage.

Figure 1: Study A6141001 Design



Children 6-16 (or younger than 6 if able to swallow pills) were eligible to be enrolled. The BP entry criterion was seated SBP greater than or equal to the 95th percentile for age, gender, and height, measured on at least three separate occasions (one historical allowed, all at least one day apart) prior to entry into the study. The BPs representing these percentiles were defined by the National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Patients who were not well controlled were eligible based on BP measurements on other treatments. Patients who were not well-controlled were to have one or more antihypertensives discontinued and then evaluated for eligibility. Randomization was stratified by age (≤12 or >12) and race, with constraints to provide approximately equal sample sizes by age and at least 25% blacks.

Concomitant antihypertensives other than potassium-sparing diuretics were allowed during the study. Potassium-sparing diuretics within seven days, as well as potassium supplements, were prohibited.

COMMENT: The study design is consistent with the WR.

6.1.4 Efficacy Findings

6.1.4.1 Study Conduct and Baseline Characteristics

Study enrollment was ended administratively after 304 subjects were randomized and assigned to study treatment. The standard deviation of the BP measurements from the 1-year safety and tolerability study, A6141077, was found to be 11.5 mm Hg, much less than the 13 mm Hg assumed in the protocol. Recalculation of power using the new estimate for variability suggested a sample of 300 subjects was sufficient to ensure greater than 90% power to detect a 5 mm Hg difference in BP change from baseline.

COMMENT: Note that the WR specifies ≥90% power to detect a 3 mm Hg difference.

Of the 393 subjects screened for the study, 304 were randomized and were treated. A total of 270 subjects (89%) completed treatment and the percentage of subjects completing both phases of the study was generally comparable across the low-dose, mid-dose, and high-dose eplerenone groups as shown in Table 2.

Table 2: Sponsor's Disposition in Study A6141001

	Number (%) of Subjects								
	High-Dose Eplerenone, mg			Mid-Dose Eplerenone, mg			Low-Dose Eplerenone, mg		
	Phase A 25-50 BID	Phase B 50 BID	Phase B Placebo	Phase A 25 BID	Phase B 25 BID	Phase B Placebo	Phase A 25 QD	Phase B 25 QD	Phase B Placebo
Screened, N=393									
Assigned to study treatment, N=304									
Treated	184	86	84	62	28	27	58	26	26
Completed	170 (92.4)	85 (98.8)	79 (94.0)	55 (88.7)	27 (96.4)	27 (100)	52 (89.7)	26 (100)	26 (100)
Discontinued	14 (7.6)	1 (1.2)	5 (6.0)	7 (11.3)	1 (3.6)	0 (0)	6 (10.3)	0 (0)	0 (0)
Other	5 (2.7)	0 (0)	1 (1.2)	3 (4.8)	1 (3.6)	0 (0)	1 (1.7)	0 (0)	0 (0)
Protocol violation	3 (1.6)	0 (0)	2 (2.4)	2 (3.2)	0 (0)	0 (0)	1 (1.7)	0 (0)	0 (0)
Withdrew consent	4 (2.2)	1 (1.2)	1 (1.2)	2 (3.2)	0 (0)	0 (0)	3 (5.2)	0 (0)	0 (0)
Drug-related adverse event	2 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.7)	0 (0)	0 (0)
Non-drug-related adverse event	0 (0)	0 (0)	1 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Analyzed for safety									
Adverse events	184 (100)	86 (100)	84 (100)	62 (100.0)	28 (100)	27 (100)	58 (100)	26 (100)	26 (100)
Laboratory data	182 (98.9)	84 (97.7)	82 (97.6)	59 (95.2)	28 (100)	27 (100)	58 (100)	26 (100)	26 (100)
Vital signs	184 (100)	86 (100)	84 (100)	62 (100)	28 (100)	27 (100)	58 (100)	26 (100)	26 (100)

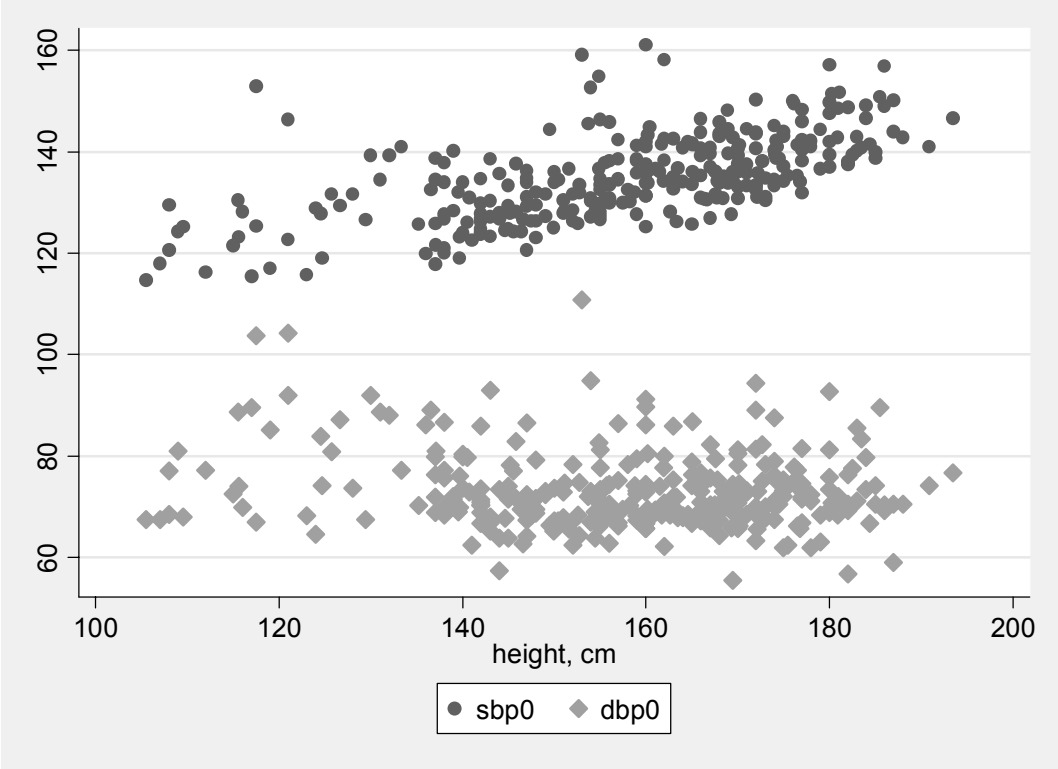
Treatment groups were comparable with respect to demographic and baseline characteristics. Subjects ranged in age from 4 to 16 years (mean age ranged from 12-13 years across treatment groups). A total of 53% of the subjects were ≤12 years of age and 47% were 13 to 16 years of age. The majority of the subjects were white (57%), followed by black (35%), and Asian (8%). The majority of subjects considered themselves to be of non-Hispanic/Latino ethnicity (89%). A total of 191 subjects (63%) were male and 113 (37%) were females. About half of the female population was menarchal (47%) and half were premenarchal (53%). The majority of patients had primary hypertension or obesity as shown in Table 3.

Table 3: Sponsor's Etiology of Hypertension for Study A6141001 Patients

	Phase A		
	High-Dose Eplerenone, mg 25-50 BID N=184	Mid-Dose Eplerenone, mg 25 BID N=62	Low-Dose Eplerenone, mg 25 QD N=58
	n (%)	n (%)	n (%)
Primary (essential)	106 (58)	31 (50)	33 (57)
Obesity	43 (23)	12 (19)	12 (21)
Renal disease	26 (14)	15 (24)	12 (21)
Other	4 (2)	3 (5)	0 (0)
Endocrine	4 (2)	1 (2)	0 (0)
Vascular disease	1 (1)	0 (0)	0 (0)
Tumor	0 (0)	0 (0)	1 (2)

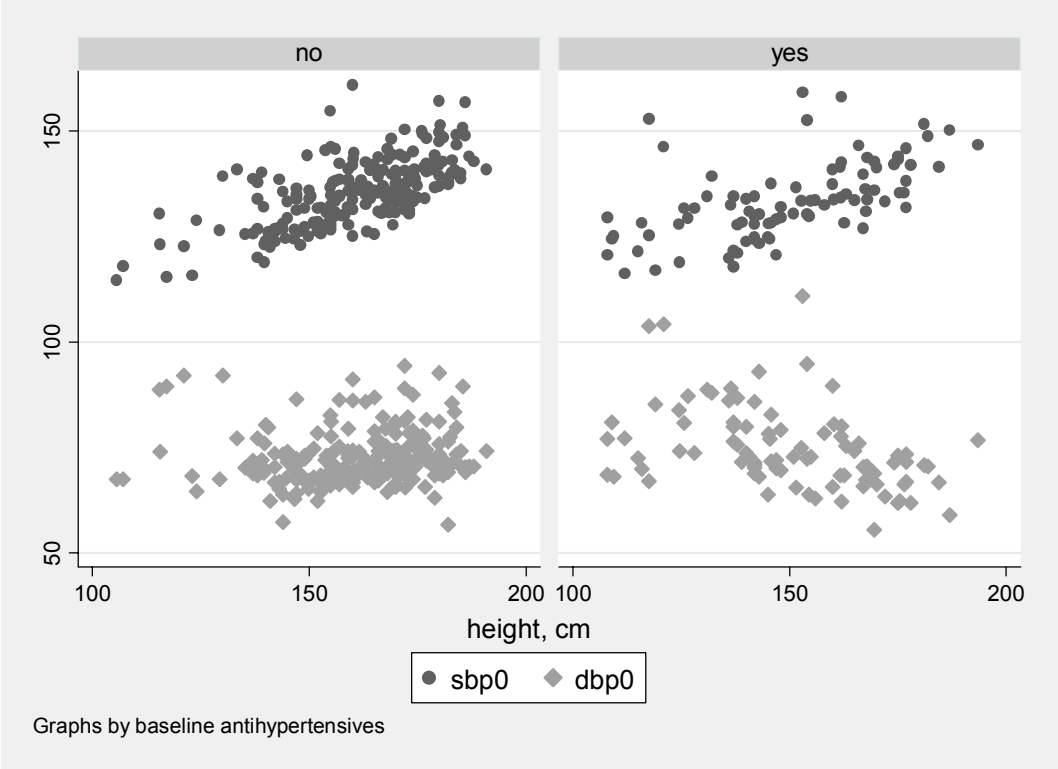
The elevations in baseline BP were modest by adult standards but significant by pediatric standards, with a mean BP of about 135/73. Because the BP entry criteria vary by age, gender, and height, the baseline SBPs show an increasing trend with increasing age or height. The trend appears to be stronger with increasing height and I show it in Figure 2.

Figure 2: Reviewer's Baseline BPs in Study A6141001 by Height



Investigators recorded that about 30% of the patients were on antihypertensives for the baseline BP measurements, slightly less for the patients older than 12 (24%) than those younger (35%). The antihypertensives most frequently used at baseline were ACE inhibitors (43%), followed by calcium channel blockers (20%) and diuretics (15%). The baseline SBPs did not appear to vary by baseline antihypertensive use while the baseline DBPs show a trend towards lower values with increasing height in those patients on baseline antihypertensives as shown in Figure 3.

Figure 3: Reviewer's Baseline BPs in Study A6141001 by Height and Antihypertensive Use



6.1.4.2 Primary Endpoint

The primary efficacy endpoint was change in SBP from baseline of phase B to the end-of-study visit, with an ordered evaluation from high dose to low dose. The primary endpoint analysis was an analysis of covariance with phase A treatment, phase B treatment, phase A/phase B treatment interaction, age strata, and race as cofactors and baseline value as covariate. The full analysis set was to include all patients randomized to phase B with last observation carried forward used for missing values. The sponsor's summary of the primary endpoint analysis is shown in Table 4.

Table 4: Sponsor's Summary of Primary Endpoint Analysis (SBP during Withdrawal) for Study A6141001

		Baseline		Treatment		LS Mean		Treatment Comparisons		
Phase B	N	Mean (SE)		Mean (SE)		Change[a] (SE)		Difference	95% CI[b]	p-value
High-Dose Eplerenone										
50 mg BID	85	128.1	(1.1)	127.0	(1.3)	-1.76	(1.1)	-2.76	-5.5, -0.0	0.0484
Placebo	84	129.7	(1.3)	131.0	(1.5)	1.00	(1.1)			
Mid-Dose Eplerenone										
25 mg BID	27	125.7	(2.3)	126.2	(2.4)	-0.04	(1.8)	2.32	-2.6, 7.2	0.3498
Placebo	27	125.4	(2.0)	124.6	(2.4)	-2.36	(1.8)			
Low-Dose Eplerenone										
25 mg QD	26	125.0	(2.1)	124.1	(2.2)	-1.49	(1.9)	-2.61	-7.6, 2.4	0.3006
Placebo	26	128.7	(2.0)	130.0	(2.0)	1.12	(1.8)			

However, note that the number of high-dose eplerenone 50 mg BID patients listed in Table 4 is 85 while the number of such patients listed in Table 2 is 86. The additional patient in Table 2 is a patient who started phase B but who discontinued the same day because of "withdrawal of consent" but who has BP values of 153-169/82-89 on that day (compared to 138-140/84-86 a week earlier.) Because that patient was treated in phase B, the patient should be included in the full analysis set (and is identified as in that set in the SAS files). If the patient is included with the last values carried forward (i.e., changes of 0 for the phase B withdrawal phase), then the p value for the high-dose group increases to 0.0664.

COMMENT: The study fails on its primary endpoint.

6.1.4.3 Other Endpoints

None of the other efficacy analyses showed statistically significant results (or even a suggestion of clinical benefit). I show the sponsor's summary of the secondary analysis of DBP during the withdrawal phase in Table 5.

Table 5: Sponsor's Summary of Secondary Endpoint Analysis (DBP during Withdrawal) for Study A6141001

		Baseline		Treatment		LS Mean		Treatment Comparisons		
Phase B	N	Mean (SE)		Mean (SE)		Change[a] (SE)		Difference	95% CI[b]	p-value
High-Dose Eplerenone										
50 mg BID	85	70.3	(0.8)	69.4	(0.9)	-0.26	(0.8)	-0.56	-2.5, 1.4	0.5753
Placebo	84	70.7	(0.8)	70.3	(1.0)	0.30	(0.8)			
Mid-Dose Eplerenone										
25 mg BID	27	70.9	(2.1)	70.9	(1.9)	0.76	(1.3)	1.18	-2.3, 4.7	0.5078
Placebo	27	70.9	(1.5)	70.1	(1.6)	-0.42	(1.3)			
Low-Dose Eplerenone										
25 mg QD	26	71.3	(1.4)	70.7	(1.6)	0.60	(1.3)	1.09	-2.5, 4.7	0.5470
Placebo	26	69.1	(1.3)	68.5	(1.1)	-0.49	(1.3)			

The Table 5 statistics do not suggest a beneficial effect of eplerenone on DBP. The changes in BP during the active treatment in phase A do not suggest a beneficial effect of eplerenone on either DBP or SBP as shown in Table 6.

Table 6: Sponsor's Summary of BP Changes during Active Treatment for Study A6141001

		Mean (SE)		Mean (SE)				Linear trend
Eplerenone	N	Baseline BP		Final BP		Change[a] (SE)		p-value
Systolic Blood Pressure								
25-50 mg BID (high dose)	170	136.3	(0.6)	128.8	(0.8)	-7.99	(0.8)	
25 mg BID (mid dose)	55	133.2	(1.1)	126.5	(1.5)	-7.84	(1.2)	
25 mg QD (low dose)	52	133.8	(1.1)	126.9	(1.4)	-7.66	(1.3)	0.8084
Diastolic Blood Pressure								
25-50 mg BID (high dose)	170	72.8	(0.6)	69.9	(0.6)	-3.05	(0.6)	
25 mg BID (mid dose)	55	74.5	(1.1)	71.3	(1.1)	-2.70	(0.8)	
25 mg QD (low dose)	52	73.6	(0.9)	69.6	(0.9)	-3.80	(0.8)	0.4050

I (and the sponsor) also examined the BP changes in phase A by dosage per kilogram and did not find any suggestion of a dose response. I also examined BP changes in both phases by other

antihypertensive use, age, gender, and race and did not find any clear signal of a differential effect in any subgroup.

COMMENT: The secondary endpoints and subgroup analyses do not suggest efficacy of eplerenone in children with hypertension.

6.1.5 Clinical Microbiology

Clinical microbiology is not applicable for an oral, antihypertensive medication.

6.1.6 Efficacy Conclusions

The sponsor's least squares mean difference of -2.8 mm Hg with a p-value of 0.0484 for SBP changes in the high-dose group compared to placebo is not very impressive. For the pre-specified analysis, i.e., including all patients treated and performing LOCF, the p-value is 0.0664, not significant. While the sponsor excluded only one patient and that patient's exclusion is consistent with the analysis set pre-specified for many antihypertensive trials (the so-called "modified intention-to-treat" consisting of all treated patients who have at least one post-treatment BP measurement), the suggestion of a beneficial effect of eplerenone in children with hypertension is marginal and not robust: The mean changes in BP among the various treatment groups in both phases appear randomly distributed and the p-values support that they are largely random. I judge that this study does not provide substantial evidence of antihypertensive efficacy of eplerenone in children.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

In study A6141077, a 15-year-old female patient with systemic lupus erythematosus (SLE) died of sepsis 40 days after withdrawing from the study. She developed heart failure and pleural effusion attributed to exacerbation of her SLE while on eplerenone 50 mg BID as well as prednisolone and azathioprine.

7.1.2 Other Serious Adverse Events

Serious adverse events (SAEs) were uncommon and diverse. In Study A6141001 five patients on active treatment (compared to three on placebo during the withdrawal) experienced SAEs: in the high dose group sleep apnea syndrome, a fall with loss of consciousness, and arthritis and pericarditis; in the mid dose group, abdominal pain; and in the low dose group pneumonia, sepsis, and pleural effusion. In Study A6141077 13 patients experienced SAEs: at 25 mg urosepsis and esophagitis, decreased serum cortisol, elevated BUN, and pregnancy (ultimately resulting in birth of a normal male infant); at 50 mg increase in estradiol and progesterone and decrease in cortisol; at 100 mg rash, nephritic syndrome relapse and pneumonia, fever, worsening of renal function and edema, palpitations, pneumonia, acute renal and heart failure and exacerbation of SLE, and peritonitis, seizures, and thrombosis of left subclavian vessels.

7.1.3 Dropouts and Other Significant Adverse Events

I show in Table 7 the sponsor's summary of patients who discontinued due to an adverse event.

Table 7: Sponsor's Patients Who Discontinued Due to an Adverse Event

Subject Number	MedDRA Preferred Term	Start Day/ Stop Day*	Severity	Outcome	Relationship to Treatment	SAE
Study A6141001						
High-Dose Eplerenone						
Phase A 25-50 mg BID:						
10821001	Hypotension	31/32	Moderate	Recovered	Definitely	
10821003	Hypertension	23/27	Moderate	Recovered	Probably	
Phase B Placebo:						
10351002	Hypertension	49/[>57]	Moderate	Still present	Unlikely	
Low-Dose Eplerenone						
Phase A 25 mg QD:						
10761001	Fatigue	1/10	Severe	Recovered	Definitely	
Study A6141077						
25 mg†:						
10392002	Hyperchlorhydria	1/3	Moderate	Recovered	Probably	No
	Vomiting	3/3	Mild	Recovered	Probably	No
50 mg†:						
10412003	Blood cortisol decreased	204/258	Moderate	Recovered	Possibly	Yes
	Estradiol increased	204/[>229]	Moderate	Still present	Possibly	Yes
	Progesterone increased	204/229	Moderate	Recovered	Possibly	Yes
10412005	Blood creatinine increased	169/220	Moderate	Recovered	Possibly	Yes
	Blood urea increased	169/197	Moderate	Recovered	Possibly	Yes
100 mg†:						
10402004	Blood creatinine increased	263/[>264]	Severe	Still present	Unlikely	Yes
10402015	Cardiac failure congestive	265/298	Severe	Death, other causes	Unlikely	Yes
	Systemic lupus erythematosus	265/[>268]	Severe	Still present	Unlikely	Yes
	Renal failure acute	265/298	Severe	Death	Unlikely	Yes
10082002	Hypertrophy breast	75/[>131]	Mild	Still present	Probably	No

Summaries of cases that are concerning are the following:

- A 10-year-old Indian male experienced in increases in serum estradiol from 68 ("reference range less than 40") to 410 pg/mL and progesterone from 0.28 to 3.42 ng/ML and a decrease in serum cortisol from 8 to 1.3 mcg/mL while on eplerenone 25 mg BID for about 200 days. Eplerenone was discontinued on day 228 and the increase in progesterone resolved quickly and the decreased in cortisol after four months, but the increase in estradiol was not resolved four months after discontinuing eplerenone.

- The breast hypertrophy AE was breast enlargement in a 15-year-old black male on 100 mg.

The sponsor also reported the following three events as of special interest: menorrhagia and late menstruation in Study A6141001 and hyperkalemia in Study A6141077. For the patient with menorrhagia concomitant medications were medroxyprogesterone acetate, prednisone, and tranemaxic acid. The menorrhagia resolved during continued treatment with eplerenone. The late (or delayed by days) menstruation in a menstruating 11-year-old also resolved during continuing treatment.

COMMENT: The two cases of gynecomastia and of sex hormonal changes in boys suggest that, even if eplerenone were demonstrated to be effective, its sex hormonal adverse effects would preclude widespread use in hypertensive children.

7.1.4 Other Search Strategies

I did not employ any other search strategies.

7.1.5 Common Adverse Events

The most frequently reported AEs were the ones typically reported most frequently in antihypertensive studies: headache (10-12%/17% short-term A6141001/long-term A6141077) and upper respiratory infections, cough, nasopharyngitis, or rhinitis (2-9%/5-8%). Because of the lack of concurrent control for most of the exposure AEs are difficult to interpret. For the more frequent events the ones that are slightly suspicious are the following: upper abdominal pain occurred in 6 high-dose patient (3%) during the active treatment phase of Study A6141001 but also was reported in 2 patients in both the placebo and active treatment of the high-dose group during the withdrawal phase. Gastritis and vomiting were reported in 4 (3%) of patients in Study A6141077. Nephrotic syndrome was reported in 4 (3%) of patients in Study A6141077.

7.1.6 Less Common Adverse Events

I cover the less common adverse events in Sections 7.1.3 and 7.1.7.

7.1.7 Laboratory Findings

There were no significant changes in mean routine safety laboratory values from baseline to end of study in Study A6141001. However, in this short study significant mean changes would not be expected. There were infrequent outlier values due to causes other than drug, e.g., one patient experienced elevated liver enzymes and subsequently was diagnosed as having viral hepatitis.

By the sponsor's analyses there were also no significant changes in mean laboratory values from baseline to end of study in Study A6141077. The sponsor's analyses included the special hormonal tests (cortisol, thyroid, and sex hormones) requested because of the mechanism of action and preclinical findings with eplerenone. However, the sponsor's analyses are not differentiated by dosage and the collection times for tests with diurnal variations, such as serum cortisol, were not controlled. I examined changes from baseline for lab tests by dosage, gender, and age and summarize the positive findings below.

For reference, before presenting the lab values as percent changes from baseline without confidence limits, I show the numbers of patients by dose, gender, and age category in Table 8.

Table 8: Reviewer's Numbers of Patients by Gender and Age Category in Study A6141077

	males		females		both	
	≤12	>12	≤12	>12	≤12	>12
25	11	13	8	6	19	19
50	9	21	7	12	16	33
100	15	37	3	7	18	44

Note that any set of lab values typically has numbers of values slightly lower than those in Table 8 because of missing values. The low numbers of patients in some groups, e.g., 3 females aged 12 or under at the 100 mg dose, limits interpretability.

The most substantial changes in lab values were for renal function and potassium. I show the mean maximum percent changes from baseline by maximum dose, gender, and age category for serum creatine in Table 9, for BUN in Table 10, and for serum potassium in Table 11.

Table 9: Reviewer's Mean Maximum Percent Changes from Baseline in Serum Creatinine by Maximum Dose, Gender and Age Category

	males		females	
	≤12	>12	≤12	>12
baseline	0.75	0.85	0.55	0.79
25	19%	13%	39%	5%
50	24%	14%	18%	36%
100	47%	17%	*	101%

*too few cases

Table 10: Reviewer's Mean Maximum Percent Changes from Baseline in BUN by Maximum Dose, Gender and Age Category

	males		females	
	≤12	>12	≤12	>12
baseline	16	13	10	13
25	18%	20%	32%	7%
50	15%	18%	9%	26%
100	29%	26%	*	105%

*too few cases

Table 11: Reviewer's Mean Maximum Percent Changes from Baseline in Serum Potassium by Maximum Dose, Gender and Age Category

	males		females	
	≤12	>12	≤12	>12
baseline	4.2	4.4	4.2	4.2
25	9%	11%	7%	12%
50	7%	11%	7%	15%
100	24%	15%	*	21%

*too few cases

The extreme mean changes for females older than 12 dosed at 100 mg were due to changes for one patient, the girl who experienced worsening SLE and ultimately died. To a lesser extent the large mean changes for males 12 or younger dosed at 100 mg were also due to one patient, a boy whose deteriorating renal function was attributed to his underlying disease (focal segmental glomerulosclerosis).

COMMENT: Eplerenone in hypertensive children, who frequently have underlying renal disease, does appear to produce moderate dose-related elevations in serum potassium and in increases in serum creatinine and BUN.

The other electrolyte, besides potassium, that eplerenone may have effected is calcium. I show the mean maximum decreases from baseline for calcium in Table 12.

Table 12: Reviewer's Mean Maximum Percent Changes from Baseline in Serum Calcium by Maximum Dose, Gender and Age Category

	males		females	
	≤12	>12	≤12	>12
baseline	9.4	9.9	9.2	9.7
25	-3%	-2%	-4%	-1%
50	-4%	-3%	-5%	-3%
100	-7%	-2%	*	-10%

*too few cases

COMMENT: Other than for males > 12, there appears to be a dose-response in decreases in calcium with increasing dosage. This may be associated with decreased alkaline phosphatase activity (not shown), but the latter is not consistent and does not show a dose-response. How these calcium changes relate to renal function changes is difficult to ascertain in this small study.

Regarding sex hormones, FSH appears to be suppressed slightly at the higher doses and ages and particularly for females as shown in Table 13.

Table 13: Reviewer's Mean Maximum Percent Changes from Baseline in FSH by Maximum Dose, Gender and Age Category

	males		females	
	≤12	>12	≤12	>12
baseline	1.8	3.3	3.0	5.8
25	7%	2%	3%	5%
50	4%	-16%	9%	-47%
100	15%	-6%	*	-55%

Changes in LH were more erratic. Changes in female sex hormones were also erratic in females, possibly due to lack of synchronization with menstrual cycles. There appears to be some suppression increases in testosterone in males as shown in Table 14.

Table 14: Reviewer's Mean Maximum Percent Changes from Baseline in Testosterone for Males by Maximum Dose and Age Category

	≤12	>12
baseline	62	302
25	157%	34%
50	82%	7%
100	24%	18%

COMMENT: The interpretation of hormonal changes is particularly hampered by the lack of a control group. However, these data suggest that eplerenone has some effects upon sex hormones. The one case of gynecomastia in a 15 year-old boy also suggests that effect upon sex hormones is a real problem. In children, these sex hormone effects are more worrisome than in adults because of concerns about sexual maturation, psychological trauma, and possible effects upon growth.

One other hormonal system showed some signs of effects from eplerenone: thyroid. I show the mean maximal changes from baseline in TSH in

Table 15: Reviewer's Mean Maximum Percent Changes from Baseline in TSH by Maximum Dose, Gender and Age Category

	males		females	
	≤12	>12	≤12	>12
baseline	2.3	1.8	2.5	1.9
25	27%	-28%	15%	-21%
50	24%	17%	61%	7%
100	89%	15%	*	19%

*too few cases

Changes in other thyroid hormones were more erratic.

COMMENT: The changes are not consistent enough to be very concerning, but there does appear to be an increase in TSH with increasing dosage, particularly in the younger children. There were no clinical cases of thyroid disease reported in this one year study, but long term effect remain unknown.

Finally, one lab value shows rather striking increases that I would not have predicted. That lab value is lactate dehydrogenase (LDH), as shown in Table 16.

Table 16: Reviewer's Mean Maximum Percent Changes from Baseline in LDH by Maximum Dose, Gender and Age Category

	males		females	
	≤12	>12	≤12	>12
baseline	249	224	267	181
25	20%	55%	52%	24%
50	57%	12%	29%	26%

	males		females	
	≤12	>12	≤12	>12
100	91%	25%	*	95%

*too few cases

COMMENT: Without a control group, the changes in LDH are difficult to interpret. There does appear to be some association of higher LDH levels with worse renal function, but the association is not consistent.

Considering all lab values, the changes that are most consistent are those in renal function, including potassium. The sex hormone changes are less consistent but perhaps more worrisome.

7.1.8 Vital Signs

I discuss changes in blood pressure in the Integrated Review of Efficacy. There were no consistent differences in heart rate in Study A6141001 for the different groups and phases.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not done routinely in these pediatric studies.

7.1.10 Immunogenicity

The sponsor did not evaluate immunogenicity nor is there any theoretical or empirical evidence suggesting that it should be studied.

7.1.11 Human Carcinogenicity

The exposure in children is too limited to evaluate human carcinogenicity.

7.1.12 Special Safety Studies

The WR specified that the long term safety study include assessments of growth (change in head circumference, weight, and length or height), and development (milestones, school performance, or neurocognitive testing) assessed at baseline and at one year. The sponsor measure height and weight and did neurocognitive testing in a substudy. The sponsor also evaluated Tanner stage and testicular volume.

Regarding age and weight, the tables in the submission include heights and weights at 1 year for only 55 patients. If the criterion for the follow-up date is relaxed to 10-14 months, then follow-up heights and weights are available for 130 patients as shown in Table 17.

Table 17: Reviewer's Numbers of Patients with Baseline and 10-14 Month Follow-up Heights and Weights

	males		females		all
	≤12	>12	≤12	>12	
25	7	10	7	5	29
50	8	19	7	11	45
100	13	34	3	6	56
any	28	63	17	22	130

As expected mean height and weight increased in all age and gender groups as shown in **Table 18** and **Table 19**.

Table 18: Reviewer's Mean Changes from Baseline in Height (cm) by Maximum Dose, Gender, and Age Category

	males		females		all
	≤12	>12	≤12	>12	
25	6.7	3.5	3.6	1.9	4.0
50	6.4	2.8	6.4	1.8	3.8
100	6.4	1.6	5.7	1.2	2.9
any	6.5	2.3	5.1	1.7	3.4

Table 19: Reviewer's Mean Changes from Baseline in Weight (kg) by Maximum Dose, Gender, and Age Category

	males		females		all
	≤12	>12	≤12	>12	
25	6.0	1.9	2.9	3.9	3.5
50	8.1	3.5	3.9	2.8	4.2
100	3.4	1.4	2.6	0.1	1.8
any	5.4	2.1	3.3	2.3	3.0

However, there is a suggestion that height increases were less in the high dose group for both males and females older than 12 and weight increases were lower in the high dose group for all ages and genders.

Regarding Tanner state, the sponsor observed that patients overall progressed in Tanner stage during the one year course of Study A6141077. Whether the progression was normal or abnormal is impossible to judge because of the lack of a control group and, because any control group would have to be treated with antihypertensives, interpretation even with a control group would be difficult.

Regarding mean testicular volume, the sponsor noted that it increased in male patients. At week 52, the mean change in testicular volume for school age boys was +2.6 mL; for adolescent boys the mean change was +2.2 mL. At end of study, the mean change in testicular volume for school age boys was +2.5 mL; and for adolescent boys, it was +1.6 mL. As for Tanner stage, interpretation is difficult without a control group.

The sponsor's summary of the neurocognitive substudy is the following: "A sub-study was conducted within Study A6141077 to assess certain cognitive functions and to document changes in cognitive function, if any, over a one-year period. In the sample, normed analyses were limited by the low percentage of US participants. At the start of the study, about 50% US subjects were expected, but challenges for enrollment resulted in only 12% [14 subjects] being US participants in the final sample. This reduced the ability to examine interaction effects with IQ and assess behavioral changes due to cultural factors affecting test administration and interpretation. Baseline scores and mean IQ scores fell within the average range and were not

clinically significant. Over the roughly 52 weeks of observation during open-label treatment with eplerenone, improvement in functioning appeared to occur on tests assessing fine motor speed and control (GP), and attentional functions (CPT-II). While improvement from Baseline to Week 52 was statistically significant on the GP, there were non-significant trends on the CPT-II with one significant improvement seen in commission errors. The CPT-II is a very sensitive measure of change over time in attentional processes and may yield fruitful results with a larger sample. The finding on the GP in these children with hypertension is consistent with previous findings in adult hypertension samples, with the suggestion that treatment of hypertension (in this case with eplerenone) results in improvement in certain cognitive functions such as fine motor skills."

COMMENT: Because of the limitations of the size, duration, and national representation in the study, any firm conclusions about effects upon growth, development, or neurocognitive functioning are impossible. I do interpret the height and weight changes as suggesting that eplerenone at high doses may have a detrimental effect upon development, but I can not state that definitively. Confounding, e.g., high dosed patients were sicker, is possible.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

During the randomized withdrawal there was no evidence of withdrawal rebound or unusual AEs. This submission does not provide data regarding abuse potential nor is there any theoretical or empirical evidence that suggests an abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

One patient in Study A6141077 was noted to be pregnant after completing the study but with an estimated time of conception 8 days prior to completion. She eventually delivered a normal male infant.

7.1.15 Assessment of Effect on Growth

See Section 7.1.12.

7.1.16 Overdose Experience

There were no overdoses reported in the pediatric studies.

7.1.17 Postmarketing Experience

There are no postmarketing AE reports in individuals <18 years old or described as a newborn, neonate, infant, child, adolescent or teenager. In addition to AEs identified in the clinical studies, the adult postmarketing experience has added possible adverse reactions of angioedema and rash.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The studies evaluable for safety in children are the last three studies listed in Table 1. They consist of a single-dose PK Study NE3-01-02-055, the double-blind efficacy Study A6141001 described in the previous section, and an open-label one-year safety Study A6141077. The latter safety study had entry criteria similar to efficacy study and, in fact, 71 of the 150 patients enrolled into the safety study from the double-blind efficacy study. One patient enrolled in the study but withdrew prior to taking study medication and was not included in any safety evaluations. Therefore, the safety population comprised 149 patients at the start. Twenty (13%) patients withdrew and 106 patients completed at least one year of treatment. The general design of this open-label safety study was simple: A six-week dose adjustment phase followed by chronic treatment to for at least one year. Potassium sparing diuretics, potassium supplements, and strong CYP3A4 inhibitors were prohibited, but "standard of care" otherwise was allowed. While eplerenone was to be titrated to 50 mg BID and could also be down-titrated, the protocol did not provide instructions on how to titrate other antihypertensives. About 46% of the patients took other antihypertensives, most commonly enalapril or amlodipine as for the efficacy study.

7.2.1.2 Demographics

I summarize the demographics for the efficacy study in Section 6.1.4.1 The demographics for the safety study were slightly different: 71% were male; 65% were white, 35% were Asian, but only 3% were black; and only 36% were 12 or younger.

7.2.1.3 Extent of exposure (dose/duration)

The extent of exposure is relatively limited: Besides the minimal one dose exposure in the PK study, the double-blind exposure in Study A6141001 was for a median duration of 42 days in phase A and 28 days in phase B; 170 patients in the 50 BID group, 55 in the 25 BID group, and 52 in the 25 QD group completed phase A. In Study A6141077 149 patients were treated initially, 129 completed, and 106 were treated for at least one year. The last dosage taken was fairly evenly distributed between the three total daily dosages: 28% at 25 mg, 37% at 50 mg, and 36% at 100 mg.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The studies in hypertensive adults are relevant to use in children. I reviewed these studies in conjunction with the original NDA submission. There is also a large outcomes study in adults with systolic dysfunction post-myocardial infarction. The safety aspects of that study also have some relevance to use in children because it included long term use. I reviewed that study in conjunction with a supplemental NDA submission.

7.2.2.2 Postmarketing experience

There are no postmarketing AE reports in individuals <18 years old or described as a newborn, neonate, infant, child, adolescent or teenager.

7.2.2.3 Literature

I searched Pubmed and found 423 references to eplerenone. However, "eplerenone and pediatric" and "eplerenone and children" yielded no references. "Eplerenone" with a limit of all children yielded seven references; all were not primarily concerned with eplerenone use in children. One described a German family with glucocorticoid-remediable aldosteronism but the abstract does not mention eplerenone treatment.

7.2.3 Adequacy of Overall Clinical Experience

The major limitation of the one year safety study is the lack of a control group. Additionally, the numbers of patients, particularly US patients, is small and one year may not be adequate for detecting problems with growth and development. Hence any negative results, while slightly reassuring, do not provided strong guarantees of long term safety. Regardless, because sufficient positive findings were demonstrated, the overall clinical safety experience is adequate for suggesting that eplerenone is not a good antihypertensive for general pediatric use.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal or in vitro testing was done.

7.2.5 Adequacy of Routine Clinical Testing

The clinical testing was adequate except for the failure to regulate collection times of day (and relationship to menstrual periods in menstruating girls) for the hormonal testing. There were few US subjects for neurocognitive testing and the overall numbers of subjects and duration of follow-up were not ideal, but see comments in Section 7.2.3 above.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The pharmacokinetic workup in children appears adequate, but please see the FDA clinical pharmacology review for a detailed discussion.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

If eplerenone showed antihypertensive efficacy in children, then a more extensive safety evaluation would be needed to support use in children. However, given the lack of efficacy and the suggestion of safety issues, I do not recommend use in children nor further study.

7.2.8 Assessment of Quality and Completeness of Data

I did not identify any problems with data quality. The completeness of the data is variable but not atypical for antihypertensive studies. It is additionally problematic because of the small sample sizes.

7.2.9 Additional Submissions, Including Safety Update

There were not additional submissions.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Eplerenone in children largely causes the same types of adverse events as those seen in adults. Increases in serum potassium and creatinine are dose-related and of particular concern in patients with reduced renal function. Eplerenone can also cause sex-hormone related AEs such as gynecomastia in males. Whether these sex-hormone effects can lead to problems with sexual development is beyond the scope of a one-year study.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

I, and the sponsor, did not pool data across studies because there were only two studies with different designs. Many patients from the first short-term trial continued into the long-term, uncontrolled open-label study.

7.4.2 Explorations for Predictive Factors

In this small safety data base many explorations for predictive factors are not feasible. I did routinely examine dose-response for adverse effects.

7.4.3 Causality Determination

Causality determination was limited by the uncontrolled nature of the long-term study.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen used for children was that approved for adults. The sponsor did not develop a new formulation for young children unable to swallow tablets. The efficacy study was too small to explore variations in dosing regimen.

8.2 Drug-Drug Interactions

Drug-drug interactions were not studied in this submission.

8.3 Special Populations

This submission addresses the special population of children. It also had high Asian and substantial black representation in the studies.

8.4 Pediatrics

This submission is a pediatric studies submission done in response to a Written Request.

8.5 Advisory Committee Meeting

Because antihypertensive efficacy was not demonstrated, I do not recommend presenting this submission to an advisory committee.

8.6 Literature Review

Please see Section 7.2.2.3.

8.7 Postmarketing Risk Management Plan
Because I do not recommend approval of use in children, I do not recommend a postmarketing risk management plan.

8.8 Other Relevant Materials
I do not know of any other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions
Because the pediatric efficacy study failed on its primary endpoint and the secondary endpoints do not provide evidence of efficacy of eplerenone in treating hypertension in children, I do not recommend that eplerenone be approved for the treatment of hypertension in children. The results of the one-year safety study suggest that eplerenone in children exhibits the same adverse effects as seen in adults, including increases in potassium and creatinine. Eplerenone also causes sex-hormone related adverse effects such as gynecomastia. Whether eplerenone has other effects in children, such as reduction in serum calcium and effects upon growth, is less clear.

9.2 Recommendation on Regulatory Action
I do not recommend that eplerenone be approved for the treatment of hypertension in children. I recommend that a brief statement regarding the failure of the study in pediatric hypertensives to show antihypertensive efficacy be included in the label.

9.3 Recommendation on Postmarketing Actions
Because I do not recommend approval I do not recommend any postmarketing actions.

9.4 Labeling Review
The sponsor proposes the following addition to the label: [redacted] In this study and in a 1-year pediatric safety study in 149 patients, the incidence of reported adverse events was similar to that of adults. INSPRA has not been studied in pediatric patients less than 4 years old."

COMMENT: The proposed label addition is acceptable.

9.5 Comments to Applicant
The sponsor should be informed that the label addition is acceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Marciniak
1/17/2008 02:28:58 PM
MEDICAL OFFICER