CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208401Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	208401
Supporting document/s:	000, 007
Applicant's letter date:	June 30, 2015; November 16, 2015
CDER stamp date:	June 30, 2015; November 16, 2015
Product:	(b) (4) (Lisinopril oral solution)
Indication:	Treatment of hypertension in adults and pediatric patients 6 years of age and older as well as for the (b) (4) signs and symptoms of systolic heart failure and for the reduction of mortality in the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction.
Applicant:	Silvergate Pharmceuticals, Inc.
Review Division:	DCRP
Reviewer:	Elizabeth Hausner, DVM, DABT, DABVT
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(NOTE: ALL TABLES AND FIGURES ARE THOSE OF THE REVIEWER UNLESS STATED OTHERWISE.)

1 Executive Summary

1.1 Introduction (and Clinical Rationale)

The sponsor presents a ready-to-use aqueous solution of lisinopril, an angiotensin converting enzyme (ACE) inhibitor, to replace the extemporaneous compounding of tablets into a suspension either by caregivers or pharmacists for patients who have difficulty swallowing tablets. The proposed indication is the treatment of hypertension in adult and pediatric patients 6 years of age and older. The other indication is for the reduction of mortality in treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction. Approval is sought under provision of section 505(b)(2) of the Food Drug and Cosmetic Act. The application relies on the Division's previous findings of safety and efficacy for the referenced drug, Zestril®(Lisinopril) tablets (NDA019777, approved May 19, 1988), distributed by Astra Zeneca Pharmaceuticals.

1.2 Brief Discussion of Nonclinical Findings

Based on preliminary meeting comments sent to the sponsor November 20, 2012 (entered into DARRTS November 29, 2012), the nonclinical sections of the Zestril package insert provide the nonclinical findings for this 505(b)(2) NDA. The sponsor also conducted a PubMed literature search for the time period of June 1, 2014 through April 9, 2015 to identify any new safety information. The June 1, 2014 date was chosen based on the last Zestril package insert update in December 2014. Searches of Toxnet and MedWatch databases for the past 12 months were also conducted but did not identify anything new compared to the PubMed search. The citations thus identified did not provide any new nonclinical safety signals.

1.3 Recommendations

1.3.1 Approvability

From the nonclinical perspective, the data supports approval.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

No changes are recommended from the non-clinical perspective.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)

83915-83-7

Generic Name

lisinopril

Code Name

Not applicable

Chemical Name

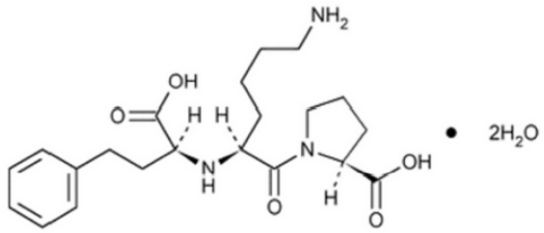
IUPAC: (2*S*)-1-[(2*S*)-6-amino-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrrolidine-2-carboxylic acid, dihydrate

N2-[(1*S*)-1-carboxy-3-phenylpropyl]-L-lysyl-L-proline, dihydrate

Molecular Formula/Molecular Weight

$C_{21}H_{31}N_3O_5.2H_2O$/ (b) (4) (441.5 (b) (4) dihydrate)

Structure or Biochemical Description



Pharmacologic Class

Angiotensin converting enzyme inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

PIND116486 lisinopril
NDA019777 for Zestril®(Lisinopril) tablets
NDA019558 for Prinvil (Lisinopril).

2.3 Drug Formulation

Lisinopril Oral Solution is a ready-to-use aqueous solution containing 1.0 mg/ml of Lisinopril. Currently, there is no FDA-approved ready-to-use oral liquid formulation of Lisinopril for pediatric patients who require weight-based dosing or older patients who have difficulty swallowing tablets.

Table 2.4-2. Composition of Lisinopril Oral Solution

Component	Grade	Function	mg/mL (% w/v)	Maximum Potency in Approved Oral Products[a]
Lisinopril dihydrate[b]	USP	Active ingredient	1.09	—
Xylitol (b) (4)	NF	(b) (4)		
Citric acid, (b) (4)	USP			
Sodium citrate, (b) (4)	USP			
Sodium benzoate	NF			
Sodium hydroxide (b) (4)	NF			
Hydrochloric acid ((b) (4)	NF			
(b) (4)	USP			

NF = National Formulary; *qs* = quantity sufficient; USP = United States Pharmacopeia; — = not applicable.

[a] = FDA Inactive Ingredient Search for Approved Drug Products; maximum potency in approved oral products (mg and/or %).

[b] = Equivalent to 1.0 mg/mL (b) (4)

[c] = Amount required to achieve pH = (b) (4)

Source: *Table 3.2.P.1-1* and *Table 3.2.P.2.1-2.*

While all values are within the Inactive Ingredient guidelines, the sponsor is inconsistent with the preparations used as guides.

- The amount listed for citric acid, (b) (4)
- The amount listed for sodium citrate (b) (4)
- The amount listed for sodium benzoate (b) (4)
- Hydrochloric acid (b) (4)

Off-label use in children less than six years of age is possible. According to the references cited in the reviewer's table below, dose may be based on either age or body weight.

Literature Based Doses of Lisinopril for Children

Age based doses	Dose range	Source of data (references)
< 6 years	0.1mg/kg body weight to 0.5 mg/kg body weight*	Meyers and Siu. Pharmacotherapy review of chronic pediatric hypertension. Clinical Therapeutics 2011. 33(10):1331-1356.
≥6 years	0.1mg/kg body weight to 0.5 mg/kg body weight*	
Body weight based doses		
<50 kg	0.625mg/day 2.5 mg/day 20 mg/day	Soffer B, et al. for the Lisinopril Pediatric Hypertension Collaborative Study Group. A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of Lisinopril for children with hypertension. American Journal Hypertension 2003. 16:795-800.
≥50 kg	1.25 mg/day 5 mg/day 40 mg/day	

There is growing attention paid to excipients used in pediatric formulations. Because this formulation has the potential to be used off-label in children younger than 6 years of age, PubMed, Toxnet, and Micromedex were searched for safety information pertaining to the excipients (Guidance for Industry: Nonclinical studies for the safety evaluation of pharmaceutical excipients, May 2005).

Depending on whether a clinician uses age-based or weight-based dosing, the exposure to the excipients will vary. The sponsor was asked to support the safety of the excipient levels in the pediatric population, in particular the population less than 6 years of age. The sponsor used weight based dosing and the following paradigm:

> Approved Drug Products database. The proposed dosage of Lisinopril Oral Solution in pediatric patients 6 years of age and older is a 0.07-mg/kg starting dose once daily (up to 5 mg total). Dosage should be adjusted, according to blood pressure response, up to a maximum of 0.61 mg/kg (up to 40 mg) once daily. The maximum exposures to xylitol, assuming the same 0.61-mg/kg high dosage is used off-label in neonates and 1, 2, 3, 4, and 5 year olds, are presented in *Table 1.11.2-1*. Each milliliter of Lisinopril Oral Solution contains 1.09 mg lisinopril, equivalent to 1.0 mg (b) (4)

The sponsor calculated potential exposure to Xylitol as shown in the following table:

Table 1.11.2-1. Potential Pediatric Exposures to Xylitol Using the Maximum Recommended Daily Dosage of Lisinopril Oral Solution				
	Mean Body Weight (kg)			
Age Group	50th Percentile	97th Percentile	Mean	Xylitol (mg)
Neonate (1 month old)	[redacted]			(b) (4)
1 Year old				
2 Year old				
3 Year old				
4 Year old				
5 Year old				
CDC = Centers for Disease Control and Prevention.				
[a] = *CDC, 2010*.				
[b] = Values calculated using the means from the tabular data 2 weeks prior and 2 weeks after the proposed yearly age (ie, the mean for 3 year olds at the 50th percentile was (b) (4) kg at 35.5 months + (b) (4) kg at 36.5 months, for a mean of (b) (4) kg at 36 months.				
[c] = *CDC, 2001*				

[redacted] (b) (4)

Xylitol is a five carbon polyol with a sweet taste said to equal that of sucrose. Xylitol is a natural constituent of fruit, is produced as part of human metabolic processes (pentose metabolism), is widely used as a sweetener and bulking agent and is not considered to be cariogenic (Touger-Decker R and C van Loveren, 2003). A beneficial modulation of bacterial colonization of the oral cavity has been reported as well as otitis media prophylaxis (Azarpazhooh et al. 2011). Because xylitol is non-absorbed in humans, sufficient amounts in the gastrointestinal tract may have osmotic consequences. Studies examining the gastrointestinal tolerance of large doses of chronically ingested xylitol indicate good tolerance even in six-month-old infants. One case report noted that repeated administration of 100 mg xylitol per kilogram of body weight to a newborn resulted in diarrhea and enteral bicarbonate loss (Wille et al. 2010).

The sponsor calculated total citrate content as the sum of sodium citrate and (b) (4) citric acid. The calculated exposures are summarized in the sponsor's table shown below.

Table 1.11.2-2. Potential Pediatric Exposures to Citrate Using the Maximum Recommended Daily Dosage of Lisinopril Oral Solution

Age Group	Mean Body Weight (kg)			Citrate (mg)
	50th Percentile	97th Percentile	Mean	
Neonate (1 month old)	(b) (4)			
1 Year old				
2 Year old				
3 Year old				
4 Year old				
5 Year old				

[a] = *CDC, 2010*.
[b] = Values calculated using the means from the tabular data 2 weeks prior and 2 weeks after the proposed yearly age (ie, the mean for 3 year olds at the 50th percentile was (b) (4) kg at 35.5 months + (b) (4) kg at 36.5 months, for a mean of (b) (4) kg at 36 months.
[c] = *CDC, 2001*.

The sponsor also notes that oral potassium citrate is used in children:

(b) (4)

Citric acid: (b) (4)

Sodium citrate (b) (4).

For the last excipient, sodium benzoate, the sponsor calculated the following table of potential exposures:

Table 1.11.2-3. Potential Pediatric Exposures to Sodium Benzoate Using the Maximum Recommended Daily Dosage of Lisinopril Oral Solution				
	Mean Body Weight (kg)			
Age Group	50th Percentile	97th Percentile	Mean	Sodium Benzoate (mg)
Neonate (1 month old)	[redacted]			(b) (4)
1 Year old				
2 Year old				
3 Year old				
4 Year old				
5 Year old				

[a] = *CDC, 2010*.
[b] = Values calculated using the means from the tabular data 2 weeks prior and 2 weeks after the proposed yearly age (ie, the mean for 3 year olds at the 50th percentile was (b) (4) kg at 35.5 months + (b) (4) kg at 36.5 months, for a mean of (b) (4) kg at 36 months.
[c] = *CDC, 2001*.

Sodium benzoate is generally regarded as safe (GRAS) and is ubiquitous in foods and medicines (Furia, 1972). Sodium benzoate is also approved in combination with sodium phenylacetate (Ammonul) for use in adult and pediatric patients to treat acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle.

According to the American Medical Association (AMA), low birthweight infants may not be able to metabolize benzoates. The AMA report notes in vitro work that suggests that benzoates compete for bilirubin binding sites on albumin. The report also notes that because of the structural similarities between salicylates and benzoate, exacerbation of peptic ulcer, mild hyperventilation, and mild respiratory alkalosis may develop. This is also found in the Ammonul label:

5.6 Hyperventilation and Metabolic Acidosis

Due to structural similarities between phenylacetate and benzoate to salicylate, AMMONUL may cause side effects typically associated with salicylate overdose, such as hyperventilation and metabolic acidosis. Monitoring of blood chemistry profiles, blood pH (b) (4) should be performed.

The caution against using salicylates in children due to the possibility of Reye syndrome may need to be considered here also. The US Pharmacopeia also notes that low birthweight infants with immature livers may not be capable of metabolizing benzoate (Appendix 1).

Sodium benzoate was mentioned by the World Health Organization (WHO) as a problem in neonates when given in conjunction with caffeine. The combination of these two chemicals was

reported to elicit non-immunological contact reactions, including urticarial and atopic dermatitis. The organization recommends a limitation on dosing sodium benzoate to neonates to less than or equal to 10 mg/kg/day due to immature metabolic capability. It was not stated how the WHO arrived at that limit.
(http://apps.who.int/prequal/trainingresources/pq_pres/workshop_China2010/english/22/002-Excipients.pdf Accessed September 4, 2015).

No information was found pertaining to the effects or lack of effects of combination of excipients in young children.

2.4 Comments on Novel Excipients

Not applicable. The excipients listed are not novel.

2.5 Comments on Impurities/Degradants of Concern

The sponsor states that the levels of USP related substances and lisinopril (b) (4) were detected at levels below the USP, ICH Q3A(R2) and ICH Q3B (R2) qualification thresholds for impurities and degradants (0.5%). " The USP website lists the following levels for qualification:

Table 1. Drug Substance Impurity Thresholds

	Impurity Thresholds
Maximum daily dose	(b) (4)
Reporting	
Identification	
Qualification	

From: www.usp.org

Table 2. Drug Product (NDA & ANDA) Degradation Product Thresholds

	Degradation Product Thresholds
Maximum daily dose	(b) (4)
Reporting	
Identification[a]	
Qualification[a]	

[a] Lower threshold may be appropriate for toxic impurities.

From www. usp.org

The ICH Q3A(R2) guidance lists the following thresholds:

Maximum daily dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
(b) (4)			

[1] The amount of drug substance administered per day
[2] Higher reporting thresholds should be scientifically justified
[3] Lower thresholds can be appropriate if the impurity is unusually toxic

Therefore the (b) (4) % limit is appropriate for the lisinopril (b) (4) but not for the impurities. The impurities, listed in the sponsor's table shown below, fall right at the threshold of requiring qualification. Guidance Q3A *Impurities in New Drug Substances* states that: "In some cases, decreasing the level of impurity to not more than the threshold can be simpler than providing safety data. Alternatively, adequate data could be available in the scientific literature to qualify an impurity."

Table 2.4-3. Potential Organic Impurities in Lisinopril (b) (4) Manufactured by (b) (4)

Impurity Name	Acceptance Criteria	Origin	Methods
(b) (4)	Not more than (b) (4) %	Synthesis by product	MTM-118
	Not more than (b) (4) %	Degradation product	
	Not more than (b) (4) %	Degradation product	
	Not more than (b) (4) %	Synthesis by product	
	Not more than (b) (4) %	Synthesis by product	
Lisinopril (b) (4) (b) (4)	Not more than (b) (4) %	Synthesis by product	

Source: *Table 3.2.S.3.2-1*.

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Adults and children, six years of age and older, for the purpose of lowering blood pressure. In adults, Lisinopril is also indicated for the treatment of signs and symptoms of systolic heart failure and for the reduction of mortality in treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction.

2.7 Regulatory Background

Lisinopril (Zestril) was originally approved May 19, 1988 under NDA 19777. This was the third angiotensin converting enzyme inhibitor (ACEI) approved in this country. Captopril was first, followed by enalapril. The sponsor was Stuart Pharmaceuticals, ICI Americas Inc (Zeneca). The regulatory history for this drug may be found http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist (accessed July 23, 2015). Lisinopril as Prinvil was approved December 29, 1987 under NDA019558. The sponsor was Merck Pharmaceuticals.
The original indication is shown here:

> PRINIVIL is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents.
> Heart Failure
> PRINIVIL is indicated as adjunctive therapy in the management of heart failure in patients who are not responding adequately to diuretics and digitalis.
> Acute Myocardial Infarction
> PRINIVIL is indicated for the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction, to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers.

There has been at least one lawsuit over the patent for this drug.

> On April 26, 2006, a trial judge of the Federal Court found that the lisinopril patent (No. 1,275,350) was valid and had been infringed by Apotex (*Merck and AstraZeneca v. Apotex*, 2006 FC 524).
>
> This patent infringement action was brought by Merck (patentee and certain related companies) and AstraZeneca (licensee) against Apotex in 1996. The parties sell lisinopril in Canada under the trademarks Apo-Lisinopril, ZESTRIL (AstraZeneca) and PRINIVIL (Merck).

The current NDA was submitted as a 505(b)(2).

3 Studies Not Reviewed

Not applicable.

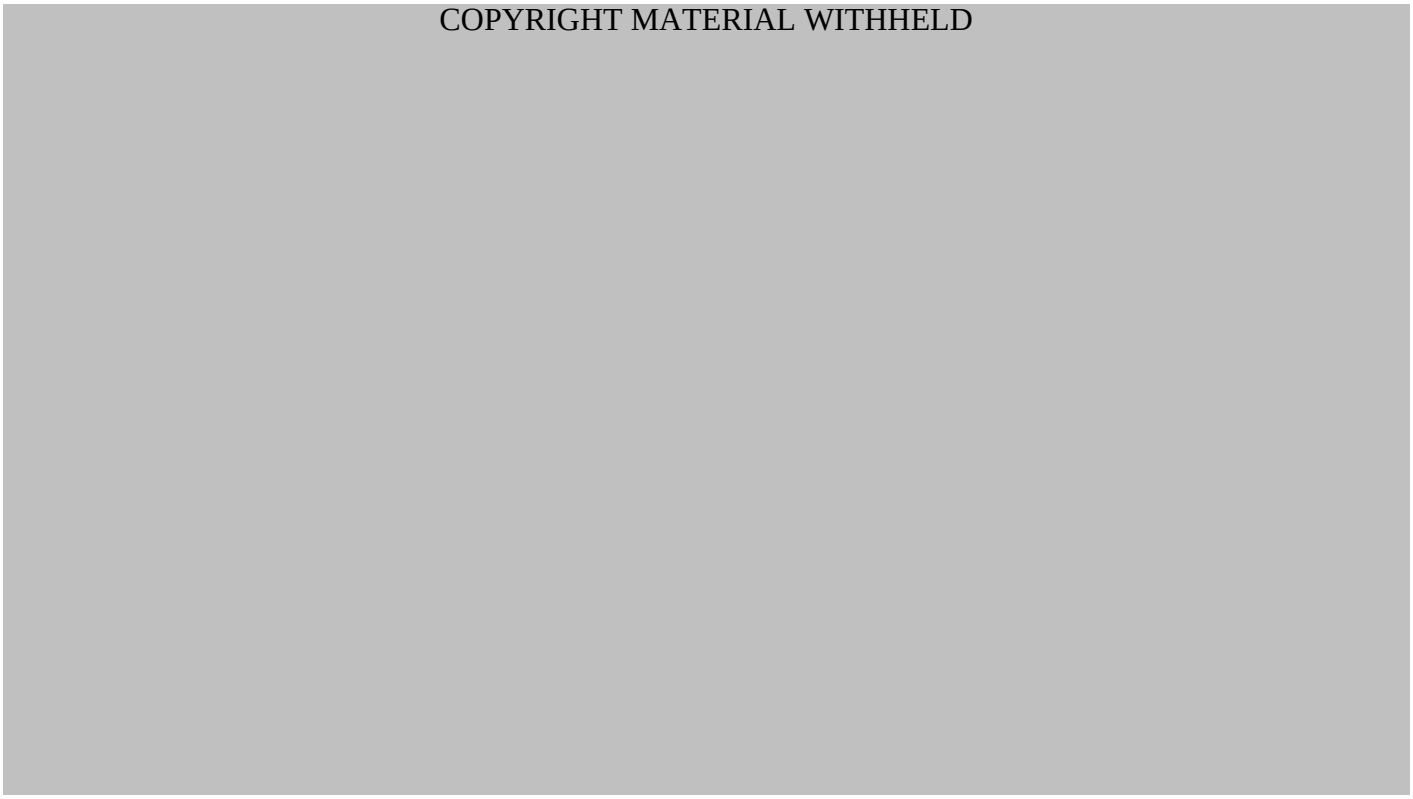
4 Pharmacology

4.1 Primary Pharmacology

Angiotensin converting enzyme is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I (AI) to the vasoconstrictor substance angiotensin II (AII). In addition, AII stimulates aldosterone secretion from the adrenal cortex. Lisinopril's beneficial effects in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone axis. Inhibiting ACE causes a decrease in plasma AII, which leads to decreased vasopressor activity and decreased aldosterone secretion. The decrease in aldosterone modulates serum electrolytes such as potassium. The many ACE inhibitors that have been synthesized are classified into three broad groups based on structure. These are 1) sulfhydryl-containing, structurally related to captopril; 2) dicarboxyl-containing, structurally related to enalapril (lisinopril falls into this group); and 3) phosphorous-containing ACE inhibitors such as fosinopril. In general, ACE inhibitors differ with regard to potency, whether the pharmacologic action is due to parent drug or a metabolite and pharmacokinetics. A detailed discussion of ACE inhibitors may be found in Goodman and Gilman's (9^{th} edition).

While the mechanism of lisinopril's blood pressure lowering is believed to be modulation of the renin-angiotensin-aldosterone-system (RAAS), lisinopril has been shown to lower blood pressure in patients with low-renin hypertension. Lisinopril is the lysine analog of enalaprilat, the active metabolite of enalapril.

ACE is identical to kininase II. Thus, Lisinopril may also block the degradation of bradykinin, a vasodilator peptide. This is also the proposed mechanism of the ACE inhibitor cough.



https://upload.wikimedia.org/wikipedia/commons/a/a2/Renin-angiotensin-aldosterone_system.png

The sponsor provides a tabular summary of several primary pharmacology studies for Lisinopril. This is shown below.

Table 2.4-5. Pharmacology: Mechanism of Action Studies					
Study	**Species/Strain**	**Number of Animals/Group**	**Route**	**Dose**	**Results**
In vitro ACE inhibitory activity[a]	Hog plasma	NS	In vitro	NA	IC_{50} = ± 0.5 nM
Augmentation of contractile response to bradykinin	Guinea pig ileum	7 segments	In vitro	NA	AC_{50} = 1.6 nM
In vivo ACE inhibition in the rat[b]	Male SD rats	8	iv	NA	ID_{50} = 2.3 (1.7-3.1) µg/kg
Duration of ACE inhibitory activity of lisinopril in rats[b]	Male SD rats	4	iv	3 and 10 µg/kg	Duration approximately 110 minutes
In vivo ACE inhibitory activity of lisinopril in conscious rats[b]	SD rats	3-5	po	0.03-3.0 mg/kg; 1 dose	Duration of at least 360 minutes
In vivo ACE inhibition in anesthetized dogs[b]	Mongrel dog	6	iv	1-30 µg/kg	ID_{50} = 6.5 µg/kg
In vivo ACE inhibitory activity of lisinopril in conscious dogs	Mongrel dog	3	po	0.05-1.0 mg/kg; 1 dose	Duration of action of between 6 and 24 hours

ACE = angiotensin converting enzyme; AC_{50} = half maximal augmented contractile response; IC_{50} = half maximal inhibitory concentration; ID_{50} = infectious dose to infect 50% of the test subjects; iv = intravenous; NA = not applicable; po = per os; SD = Sprague Dawley.
[a] = Inhibition of enzymatic activity of hog plasma ACE using ^{14}C labeled substrate.
[b] = Blockage of functional (pressor) response to A1 challenge.
Source: *Zestril product monograph, 2014.*

Table 2.4-6. Pharmacology: Effects on Blood Pressure					
Study	**Species/ Strain**	**Number of Animals/Group**	**Route**	**Dose**	**Results**
Antihypertensive activity in renal hypertensive dogs (single doses)	Mongrel dog	3	po	0.3 mg/kg with and without HCTZ	After 2 hours: Lisinopril alone: 5% reduction in mean systolic pressure vs pretreatment. Lisinopril + HCTZ: 11% reduction in mean systolic pressure vs pretreatment.
Antihypertensive activity in rats on a sodium-deficient diet	Male SD rats	5	po	0.03-3.0 mg/kg daily for 4 days	After 2 hours: 11% reduction in mean systolic pressure vs pretreatment at 1 mg/kg. Twenty-two percent reduction in mean systolic pressure vs pretreatment at 3 mg/kg. Consistent response over 4 days.
Antihypertensive activity in 2 kidney Grollman hypertensive rats (single doses)	Male SD rats	6-7	po	1 and 3 mg/kg	At 2 hours: approximately 6% reduction in mean systolic pressure vs pretreatment with the antihypertensive effect lasting up to 24 hours.
Antihypertensive activity in SH rats with and without HCTZ	SH rats	3-6	po	1.25 mg/kg HCTZ = 50 mg/kg daily for 3 days	Enhancement of hypotensive activity over 3-5 days. Two hours after drug administration, lisinopril alone reduced the average mean arterial pressure from 198 to 161 mmHg. In combination with HCTZ, the average mean arterial pressure was reduced from 202 to 132 mmHg.

Table 2.4-6. Pharmacology: Effects on Blood Pressure					
Study	**Species/ Strain**	**Number of Animals/Group**	**Route**	**Dose**	**Results**
Antihypertensive activity in SH rats (single doses)	SH rats	3-9	po and iv	0.1-20 mg/kg	Slight fall in blood pressure at 0.312 to 5 mg/kg po. Pronounced fall at 20 mg/kg po and 0.1 mg/kg iv with statistically significant reductions being observed for the majority of time points between 1/2 to 18 hours.
HCTZ = hydrochlorothiazide; iv = intravenous; po = per os; SD = Sprague Dawley; SH = spontaneously hypertensive; vs = versus. Source: *Zestril product monograph, 2014.*					

4.2 Secondary Pharmacology

Information was not provided about secondary pharmacology. A search of Google and PubMed did not reveal any published information. The years of clinical experience with Lisinopril minimize the need for this information.

4.3 Safety Pharmacology

Safety pharmacology information was not provided. The years of clinical experience with Lisinopril minimize the need for this information.

5 Pharmacokinetics/ADME/Toxicokinetics

There are several decades of clinical experience with Lisinopril, including published reports of the pharmacokinetics in several age groups of children.

5.1 PK/ADME

Absorption
According to Goodman and Gilman, 9th edition, Lisinopril is slowly, variably and incompletely absorbed after oral administration at approximately 25%. Peak plasma concentrations are achieved in approximately 7 hours.

Distribution
No or minimal tissue accumulation is reported.
Studies in rats indicate that Lisinopril crosses the blood-brain barrier poorly. Multiple doses of lisinopril in rats do not produce tissue accumulation. The milk of lactating rats contains radioactivity following administration of ^{14}C-lisinopril. Whole-body autoradiography demonstrated radioactivity in the placenta following administration of radiolabelled drug to pregnant rats.

Metabolism
There appears to be little, if any, metabolism.

Excretion
The drug is cleared as the parent compound by the kidney and the half-life in plasma is approximately 12 hours after multiple dosing. Impaired renal function decreases elimination of Lisinopril. This becomes clinically important when the glomerular filtration rate is below 30 ml/min/1.73m^2.

Protein Binding
Little protein binding is demonstrated.

According to the package insert of Zestril, the pharmacokinetics of Lisinopril has been studied in 29 pediatric hypertensive patients between 6 and 16 years of age with glomerular filtration rates

greater than 30 ml/min/1.73m^2. The plasma concentrations reported and the extent of absorption based on urinary recovery of approximately 28% were similar to the values reported for adults.

5.2 Toxicokinetics

See above.

6 General Toxicology

6.1 Single-Dose Toxicity

Five acute toxicity studies were conducted in three different species by three different routes of exposure. These are summarized in the sponsor's table below:

Table 2.4-7. Acute Toxicity of Lisinopril

Route	Species	Gender	LD_{50} (g/kg)
Oral	Mouse	Male	> 20
	Mouse	Female	> 20
	Rat	Male	> 20
	Rat	Female	> 20
	Dog	Male	> 6
	Dog	Female	> 6
Intravenous	Mouse	Male	> 10
	Mouse	Female	> 10
Intraperitoneal	Rat	Male	> 10
	Rat	Female	> 10

LD_{50} = median lethal dose.
Source: *Zestril product monograph, 2014.*

Route of administration	species	Reported signs
oral	mice	Decreased activity, death (1 out of 10 males)
oral	rats	No signs reported
oral	dogs	Diarrhea, increased serum urea nitrogen
intravenous	mice	Bradypnea, ataxia, convulsions, exophthalmia, tremors
intraperitoneal	rats	Ataxia, death (1 out of 10 females). No signs reported for the male rats

6.2 Repeat-Dose Toxicity

The referenced repeat dose toxicology studies include: six studies in rats, seven studies in dogs, and 1 study in rabbits. The sponsor's summary tables are shown below.

Table 2.4-8. Subchronic and Chronic Repeat-dose Toxicology Studies with Lisinopril

Species	Duration	Number of Animals/Group	Route	Dose (mg/kg/day)	Effects
Rat	2 weeks	10 males 10 females	Oral	3, 10, 30	At all doses, decreases of 2% to 16% in weight gain and 12% to 14% in heart weights were observed in female rats.
Rat	3 months with 1 month interim	25 males 25 females	Oral	3, 10, 30	At all doses, increased serum urea nitrogen values (up to approximately 2-fold) and decreased heart weights (7% to 10%) were observed in female rats. At 10 and 30 mg, weight gain decreased 11% and 14%, respectively, in males. An increased incidence of focal erosions of the gastric mucosa and focal renal tubular basophilia were also seen.
Rat	1 year with 6 months interim	25 males 25 females	Oral	2, 5, 10, 30, 90[a]	At all doses, a decrease in weight gain (up to 16%) was observed. Serum urea nitrogen increased up to 4-fold, serum sodium decreased (average down to 3 mEq/L), and serum potassium increased (average up to 0.5 mEq/L). At 2, 5, 10, and 30 mg, heart weight decreased; at 5, 10, and 30 mg, kidney weight increased; and at 5, 10, 30, and 90 mg, renal tubular basophilia increased. At 10, 30, and 90 mg, focal interstitial nephritis was observed.
Rat	3 months with a 1-month interim and a 1-month recovery	30 males 30 females	Oral	3, 30, 300, 3000	At all doses, weight gain decreased by 5% to 11%, and increases were observed in serum urea nitrogen (up to approximately 3-fold) and serum potassium (average up to 0.4 mEq/L). At 30, 300, and 3000 mg, there was an increased incidence of focal tubular basophilia that persisted in rats given 300 or 3000 mg/kg/day.
Rat	1 month	15 males 15 females	Oral	30, 60, 30 (+ saline), 60 (+ saline)	Saline supplementation prevented decreased weight gain and elevations in serum urea nitrogen at 30 and 60 mg. Decreases in cardiac weight at 30 and 60 mg were suppressed by saline supplementation in males at 30 mg. At 30 and 60 mg, renal changes (renal tubular degeneration and renal tubular basophilia) produced due to a low-salt diet were prevented by saline supplementation. Mild gastric erosions or necrotic changes were seen in 1 or 2 of 30 rats given 30 or 60 mg. These gastric changes were not seen in saline-supplemented animals given these doses; however, the relationship of amelioration due to saline is uncertain because of the low incidence of this change, which is also occasionally seen in untreated animals.
Rat	5 days with 6 days recovery	8 males	Oral	5, 300	Consumption of 2% saline increased during treatment at 5 mg and on days 2 to 4 post-treatment at 300 mg.

Table 2.4-8. Subchronic and Chronic Repeat-dose Toxicology Studies with Lisinopril

Species	Duration	Number of Animals/Group	Route	Dose (mg/kg/day)	Effects
Dog	2 weeks	3 males 3 females	Oral	3, 10, 30	At 30 mg, slight mineralization of the papillary muscle of the heart was seen in 1 of 6 dogs.
Dog	3 months with 1 month interim	5 males 5 females	Oral	3, 10, 30	At 10 mg, hemoglobin concentration, hematocrit, and erythrocyte count decreased in 2 dogs. Marked increases in serum urea nitrogen and creatinine were observed in 2 of 10 dogs. One of these dogs had marked renal tubular degeneration and ulcers of the tongue, gums, and gastric pyloric mucosa related to uremia. At 30 mg, there was an increase in serum urea nitrogen (average up to 2-fold) and a decrease in serum sodium (down to 4 mEq/L) and serum chloride (down to 3 mEq/L). At 10 and 30 mg, average cardiac weight decreased (13% to 15%).
Dog	1 year with 6 months interim	5 males 5 females	Oral	3, 5, 15	At 15 mg, increases were observed in serum urea nitrogen (less than 2-fold). Decreases in serum sodium (average down to 2 mEq/L) and increases in serum potassium (average up to 0.5 mEq/L) occurred at all doses.
Dog	18 days	3 males 3 females	Oral	60/90 with and without saline	Saline supplementation prevented increases in serum urea nitrogen in dogs given 60 mg for 8 days followed by 90 mg for 8 or 9 days.
Dog	7 days	4 males 4 females	iv	60, 90	Decreases in blood pressure and increases in serum urea nitrogen occurred in dogs given 60 or 90 mg/kg/day. Supplementation with physiologic saline (25 mL/kg 1 hour prior to dosing and 4 hours after dosing) prevented these changes. Increased serum potassium (average up to 0.6 mEq/L) and decreased serum chloride (average down to 0.4 mEq/L) values were seen in both supplemented and unsupplemented animals.
Dog	1 month	2 males 2 females	Oral	3, 30, 300, 1000	At 30 mg or greater, BUN increased and specific gravity of the urine decreased. Hyperplasia of renal epithelial cells was observed and deaths occurred. Dogs that died had dilation of distal renal tubules and fatty degeneration of the epithelium. No drug-related effects were observed at 3 mg.
Dog	3 month with 1-month recovery (high dose)	Control 5 males 5 females 3, 10, and 30 3 males 3 females 100 8 males 8 females **Recovery** Control 2 males 2 females 100 5 males 5 females	Oral	3, 10, 30, 100	Eight of 16 dogs given 100 mg died or were euthanized because of poor physical condition. One of 6 dogs given 30 mg was euthanized because of poor physical condition. At 10 mg or greater, increased BUN and dilation of renal tubules was seen. Fatty degeneration of renal tubular epithelium occurred at the 2 highest dosage levels. The changes are reversible because only slight dilation of renal tubules was present in some animals given 100 mg after 4 weeks of recovery.

Table 2.4-8. Subchronic and Chronic Repeat-dose Toxicology Studies with Lisinopril

Species	Duration	Number of Animals/Group	Route	Dose (mg/kg/day)	Effects
Rabbit	2 weeks	6 females	Oral	15 (1,6, and 13 doses) with and without saline	Renal tubular basophilia and renal tubular dilation (considered sequela to necrosis) were seen after 6 and 13 doses in unsupplemented rabbits. Two supplemented rabbits (6 doses) also had the same renal lesion. One rabbit drank very little saline and had increases in BUN, creatinine, and potassium. Increases in these parameters were seen in unsupplemented animals after 1, 6, and 13 doses.

BUN = blood urea nitrogen; mEq/L = milliequivalents per liter.
[a] = Dosing terminated week 11, rats euthanized week 27.
Source: *Zestril, product monograph, 2014.*

7 Genetic Toxicology

According to the Zestril package insert, Lisinopril was not mutagenic in the Ames assay either with or without metabolic activation. Lisinopril did not produce forward mutations in either a Chinese hamster lung cell assay, nor did it produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. There was no indication of positive genotoxicity in the chromosomal aberration assay in Chinese hamster ovary cells nor in the in vivo mouse bone marrow (micronucleus) assay.

7.2 Other Genetic Toxicity Studies

Not applicable.

8 Carcinogenicity

Lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 or 9 times the maximum recommended daily adult human dose based on body weight and body surface area, respectively). A tumorigenic effect was not apparent in this study.
No carcinogenic effect was detected in the mouse study when Lisinopril was administered for 92 weeks to male and female mice at doses up to 135 mg/kg/day (about 84 times the maximum recommended daily adult human dose based on body weight). Based on body surface area in mice, this dose was approximately 6.8 times the maximum recommended adult dose.

Several other effects were reported from the long term toxicology studies. These included focal sacculations of retinal vessels in rats given 30 or 90 mg/kg/day compared to the control rats. An additional 105 week study was conducted in rats using doses of 1, 3, and 10 mg/kg/day. Several renal-associated effects were reported. These included increased incidence of renal tubular hypertrophy in male rats given 3 or 10 mg/kg/day. Increased incidence of chronic nephritis in the females was seen in the carcinogenicity study. The no effect dose was determined in the second 105 week study to be 10 mg/kg/day.

9 Reproductive and Developmental Toxicology

Segment I

There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of Lisinopril. This dose is up to 30 times the maximum recommended adult human dose based on body surface area.

Segment II

Mice: Given doses up to 1000 mg/kg from GD6 through GD15. Increased fetal resorptions from doses ≥100 mg/kg. At doses of 1000 mg/kg this was prevented by saline supplementation.

Rats: given doses up to 300 mg/kg from GD 6 through GD17. There was no fetotoxicity or teratogenicity reported.

Rabbits: given doses up to 1 mg/kg "through the organogenic period." Specific dates were not provided. The rabbits were saline supplemented as rabbits have been demonstrated to be very sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternally toxic and fetotoxic effects apparent at or below the recommended therapeutic dosage levels. Fetal resorptions were increased at an oral dose of 1 mg/kg Lisinopril. Increased incidence of incomplete ossification was reported at the lowest dose tested (0.1 mg/kg/day).

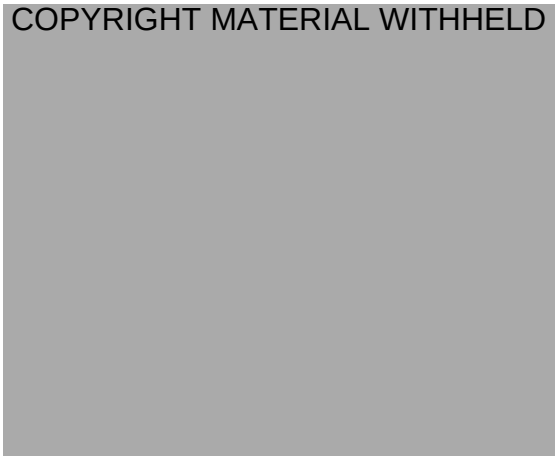
Rabbits: a single intravenous dose of 15 mg/kg of Lisinopril administered on gestation days 16, 21, or 26 resulted in 88-100% fetal death.

Segment III
Rats receiving Lisinopril from GD15 through day 21 postpartum showed an increase in pup deaths on days 2 to 7 postnatal. A lower average body weight of pups was also reported for postnatal day 21. Saline supplementation to the dams was reported to prevent the pup deaths and decreased body weights. No further details were provided about the post-natal phase.

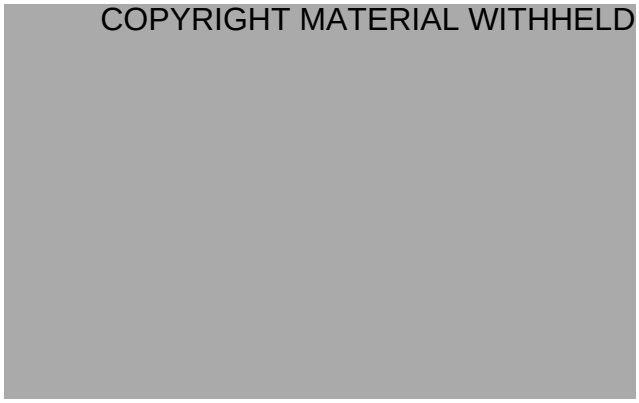
11 Integrated Summary and Safety Evaluation

The subject of the current NDA is a ready-to-use Lisinopril oral solution for pediatric patients six years of age or older and adult patients who have difficulty swallowing tablets. This is proposed to replace the current practice of crushing tablets and mixing with a palatable fluid or food (extemporaneous compounding) performed either by caregiver or other.

Lisinopril is an approved anti-hypertensive medication that works by inhibition of angiotensin converting enzyme (ACE). There are several decades of clinical experience with this drug, including the use in children. The published literature does not indicate any new safety concerns. This is mildly qualified by the usual lack of prospective studies examining growth and development. The brief discussion of rats receiving Lisinopril from GD15 through post-natal day 21 did not include details of growth and development. Raes et al (2007) also mention the need for prospective assessment of lisinopril on growth and development in the paragraph shown alongside:



The methods of administering Lisinopril to children were discussed in the published literature as shown below:



From Raes et al. Lisinopril in pediatric medicine: a retrospective chart review of long-term treatment in children. J RAAS 2007.8:3-12.

This is not a phenomenon unique to the case review that Raes et al. conducted. Zgraggen et al. (2012) and Ferrarini et al. (2013) note a lack of formulations appropriate for childhood. Parents crush tablets and administer the antihypertensive drug mixed with solid food or a palatable drink. The opportunity for inappropriate dosing or for mixing the drug with a food or drink that is incompatible with the drug substance is very real. A liquid dosing form of Lisinopril has been explored before (Nahata and Morosco. 2004). The development of a liquid formulation for the pediatric population seems to meet a defined need and should help to address the safety issues associated with extemporaneous formulations.

The sponsor has provided reasonable support for the levels of excipients in the proposed formulation. The remaining concern is for low birth weight infants requiring high doses of Lisinopril.

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(b) (4)

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APPENDIX 1: Excipient Information Obtained From ToxNet

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[American Medical Association. AMA Drug Evaluations Annual 1991. Chicago, IL: American Medical Association, 1991., p. 2034] **PEER REVIEWED**

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[US Pharmacopeial Convention; US Pharmacopeia Dispensing Information (USP DI); Drug Information for the Health Care Professional 12th ed, V.I p.2475 (1992)] **PEER REVIEWED**

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