APPLICATION NUMBER:

208401Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW
Cross-Discipline Team Leader Review

**Date**
July 17, 2016

**From**
Aliza Thompson

**Subject**
Cross-Discipline Team Leader Review

**NDA #**
208401

**Applicant**
Silvergate Pharmaceuticals, Inc

**Date of Submission**
June 30, 2015

**PDUFA Goal Date**
July 30, 2016 (extended from April 30, 2016 because of a major amendment)

**Proprietary Name / Established (USAN) names**
Qbrelis / Lisinopril Oral Solution

**Dosage forms / Strength**
Oral Solution / 1 mg/ml

**Proposed Indication(s)**
1. for the treatment of hypertension in adult patients and pediatric patients 6 years of age and older to lower blood pressure
2. to reduce signs and symptoms of systolic heart failure
3. for the reduction of mortality in treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction

**Recommended:**
Approval

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1. Introduction

On June 30, 2015, Silvergate Pharmaceuticals, Inc. submitted a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Qbrelis (lisinopril) Oral Solution for the following proposed indications:

- for the treatment of hypertension in adult patients and pediatric patients 6 years of age and older to lower blood pressure;
- to reduce signs and symptoms of systolic heart failure;
- for the reduction of mortality in treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction.

The application relies on the Agency’s previous finding of safety and effectiveness for the reference listed drug, Zestril® (lisinopril) tablets (NDA 019777, approved May 19, 1988), distributed by AstraZeneca Pharmaceuticals. The main issue that arose during review of the application was the product’s orphan designation for the treatment of pediatric hypertension, a designation that was both granted and withdrawn during the course of the review (see Section 11 for further discussion). From a CMC, non-clinical pharmacology-toxicology, clinical pharmacology, and clinical safety and efficacy perspective, the application can be approved.

2. Background

Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor. The reference listed drug, Zestril® (lisinopril) tablets, is indicated for the same indications proposed for Qbrelis (lisinopril) Oral Solution. At present, there is no FDA-approved oral liquid formulation of lisinopril. Silvergate’s product is intended to address the need for a liquid formulation of lisinopril that can be used in pediatric patients 6 years of age and older with hypertension and adults who have difficulty swallowing solid oral dosage forms.

3. CMC/Device

OPQ recommends approval of the application from a quality perspective. There are no unresolved issues at this time and no phase 4 commitments are needed.

*Drug Substance:* Lisinopril is a synthetic peptide derivative that is manufactured as a dihydrate and is chemically described as \(1\text{-}[N^2\text{-}(S)\text{-1-Carboxy-3-phenylpropyl})\text{-L-lysyl}]\text{-L-proline dihydrate. Lisinopril is a white to off-white, crystalline powder that is soluble in water, sparingly soluble in methanol, and practically insoluble in ethanol. Its molecular weight, molecular formula and structural formula are shown below.}

Molecular formula: \(C_{21}H_{31}N_3O_5\cdot2H_2O\)

Molecular weight: 441.52 (for dihydrate)
Structural formula:

![Chemical Structure](image)

**Drug Product:** The drug product is a ready-to-use aqueous formulation. Each 1 mL of the solution contains 1.09 mg of lisinopril dihydrate, equivalent to 1 mg of lisinopril as the active ingredient. The product, which is packaged in 150 mL bottles, is a clear to slightly opalescent liquid. Inactive ingredients include: purified water, xylitol, sodium citrate, citric acid, sodium benzoate, and either hydrochloric acid or sodium hydroxide (added for pH adjustment).

**Expiration Date and Storage Conditions:** According to the Quality Assessment, the proposed shelf-life (expiration dating period) of 24 months is acceptable. The proposed storage conditions for the drug product (controlled room temperature 20°C-25°C (68°F-77°F) and protected from freezing and excessive heat) are also acceptable.

**Facilities review/inspection:** The manufacturing facilities were found to be acceptable based on their inspectional histories and reviews during pre-approval inspections.

### 4. Nonclinical Pharmacology/Toxicology

The application may be approved from a nonclinical perspective. The application is relying on the nonclinical sections of the package insert for Zestril® (lisinopril), the reference listed drug. According to Dr. Hausner’s review, the applicant also conducted a PubMed literature search and searches of the Toxnet and MedWatch databases. These searches did not identify any new nonclinical safety signals.

### 5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology recommends approval of the application from a clinical pharmacology perspective. As previously noted, the application relies on the Agency’s previous finding of safety and effectiveness for the reference listed drug, Zestril® (lisinopril) tablets (NDA 019777, approved May 19, 1988), distributed by AstraZeneca Pharmaceuticals. The clinical pharmacology review focused on the findings in two randomized crossover bioequivalence studies of lisinopril oral solution (10 mL x 1 mg/mL) and Zestril® tablets (10 mg). These studies were conducted in healthy subjects in the fasted state (Study SG03-01) and
fed state (Study GS03-02) and were performed to establish a bridge between the applicant’s product and the reference listed drug.

As shown in the tables below, taken from the clinical pharmacology review, the geometric mean ratios of the exposure measures of Cmax and AUC0-t and the respective 90% confidence intervals in both studies were within the 80 to 125% bioequivalence limits, indicating bioequivalence of the oral solution and 10 mg Zestril® tablet in the fasted and fed state.

**Figure 1:** Geometric mean ratios and 90% confidence intervals for the exposure parameters for lisinopril oral solution as compared to the Zestril tablet in the fasted state (Study SG03-01)  
*Source: Office of Clinical Pharmacology Review, page 12*
Figure 2: Geometric mean ratios and 90% confidence intervals for the exposure parameters for lisinopril oral solution as compared to the Zestril tablet in the fed state (Study GS03-02)
Source: Office of Clinical Pharmacology Review, page 29

Inspections: The review team requested Biopharmaceutical Inspections of the clinical and analytical site. The inspection pertaining to the clinical portions of the submitted bioavailability studies (SG03-01 and G03-02) did not identify any significant deficiencies, and, according to the Division of Generic Drug Bioequivalence Evaluation memo, the data from the clinical portions of these studies may be accepted for review. The Division of New Drug Bioequivalence Evaluation recommended accepting the data from the analytical site without an on-site inspection because the site was recently inspected and classified as No Action Indicated.

6. Clinical Microbiology

The product is not an antimicrobial. According to the Quality Review, the microbial limits & antimicrobial effectiveness testing specifications are acceptable from a Product Quality Microbiology perspective.
7. Clinical/Statistical- Efficacy

As discussed under Clinical Pharmacology, bioequivalence studies conducted in the fed and fasted stage demonstrate that the oral solution is bioequivalent to 10 mg Zestril® tablet.

8. Safety

As previously noted, the application is relying on the Agency’s previous determination of safety for the reference listed drug, Zestril® (lisinopril). The application also contains information on the safety findings in studies SG03-01 and SG03-02, safety findings as reported in the published literature, and the results of a FAERS search.

Findings in Studies SG03-01 and SG03-02

The submission contains data on a total of 111 subjects who received a single dose of Lisinopril Oral Solution under fed conditions (Study SG03-02) or fasted conditions (Study SG03-01). Review of the safety data from these studies does not raise any safety concerns. There were no deaths, serious or severe adverse events or adverse events leading to study drug discontinuation. Headache was the most frequently reported AE and was reported at a similar incidence following administration of the oral solution and tablet formulation. No other TEAEs were reported in more than 1 subject per treatment group.

Literature Search

The applicant conducted a literature search to better characterize the safety profile of lisinopril in children. Two studies describing the safety of lisinopril in children with hypertension were identified. These studies enrolled a total of 238 children between the ages of 2 months to 17.7 years. One of these studies, a study by Soffer et al published in 2003 in the American Journal of Hypertension, appears to be the pediatric study that is described in the Zestril label. The other study, published by Raes et al in 2007 in the Journal of the Renin- Angiotensin-Aldosterone System, was a retrospective chart review of data from 123 patients age 2 months to ~17 years treated with lisinopril (median dose of ~0.11 mg/kg/day) at a single pediatric nephrology clinic over an approximately 9-year period. Of the patients included in the chart review, 59 had a diagnosis of hypertension; the mean duration of treatment was 2 years. According to the paper:

- Five of the 123 patients died during follow-up. Based on the reported causes of death, none of these deaths appeared to be related to treatment with lisinopril.
- Six patients discontinued treatment because of an adverse event. The paper indicates that in one patient “…the cause was hypotension and headache and as this diabetic had good glycaemic control with low risk of nephropathy it was decided to discontinue lisinopril,” but does not otherwise identify the adverse events that led to treatment discontinuation.
- A total of 129 adverse events were identified and of these, 20 were considered to be possibly related to lisinopril treatment. Hypotension was reported to be the most common adverse event.
• Mean hematology and creatinine and potassium values were not affected by lisinopril treatment.

The authors conclude that lisinopril was well-tolerated at the doses studied in this population.

**Reviewer’s comment:** The findings, as reported in the paper, do not raise concern; however, limited detail is provided.

In addition to conducting a review of the published literature on the experience with lisinopril in children, the applicant also conducted a literature review focused on safety findings in adults since the most recently published label for Zestril. These studies, which were conducted in patients with hypertension and in patients with hypertension who also had underlying renal disease, do not raise new safety concerns.

**Spontaneous adverse event reports**

The applicant searched the FAERS database for adverse drug experiences involving the use of various lisinopril formulations over a 9-month period from January 2014 through September 2014. According to the applicant, there were 8 cases reported in patients < 17 years of age where lisinopril was listed as the primary suspect for causing the adverse event. Per the applicant, all of the cases involved hypotension, occurred in patients ≤ 2 years of age, and reflected off-label use (information on what the drug was being used for is not provided). Three cases of bradycardia and 1 case of tachycardia were also reported in these patients.

During this same period, there were 666 cases in patients 17 years of age and older in which a product containing lisinopril was listed as the primary suspect for causing the adverse event. The submission reports the 25 most frequently reported adverse events; review of these adverse events does not raise new safety concerns. Angioedema and adverse events that could reflect angioedema were among the most common events reported. Hyperkalemia, renal failure acute, cough and hypotension were also reported. Of note, the current lisinopril label contains Warnings and Precautions related to angioedema, hyperkalemia, renal impairment and hypotension and cough is described in Section 6 of the label. Completed suicide was the second most frequently reported adverse reaction; what to make of this is unclear.

**9. Advisory Committee Meeting**

The application does not raise significant issues regarding the safety or effectiveness of the drug; hence, no Advisory Committee Meeting was held.

**10. Pediatrics**

The applicant has requested a waiver for pediatric studies for the (1) the treatment of signs and symptoms of heart failure and (2) the reduction of mortality in treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction. The Division and PeRC agree that a waiver should be granted for these indications because studies are impossible or highly impractical.
In its pediatric assessment, submitted in April 2016, the applicant requested a partial waiver of studies in pediatric patients less than 2 years of age with hypertension and a deferral in patients with hypertension age 2 to 6 years of age. Both the Division and PeRC agree with the request. Because the reference listed drug for this 505(b)2 application is already approved for the treatment of hypertension in pediatric patients > 6 years of age, studies are not needed in pediatric patients > 6 years of age. The following rationale for issuing a partial waiver for the treatment of hypertension in pediatric patients less than 2 years of age is given in the Division’s memo to the PeRC:

“In humans, nephrogenesis is thought to be complete around birth; however maturation of other aspects/functions of the kidney (such as glomerular filtration and tubular function) continues after birth. An outstanding question as relates to the use of ACE inhibitors (and other RAS inhibitors) is whether using these agents before renal maturation is complete has long-term deleterious effects on the kidney. We believe this question would be difficult (if not impossible) to resolve in a feasible clinical trial; hence, we have reached the conclusion that we should not require studies under PREA for ACE inhibitors or ARBs for the treatment of hypertension in pediatric patients under 2 years of age.”

Reviewer’s comment: Although we reached this conclusion after significant discussion, I think it is fair to say that no one considers this to be a satisfying resolution to the issue. Moving forward, it will be important to engage in further discussion with the community about the larger issue of evaluating the efficacy and safety of RAS inhibitors as a treatment for hypertension in the very young.

11. Other Relevant Regulatory Issues

**Orphan Drug Designation for the treatment of pediatric hypertension:** FDA granted orphan designation for lisinopril oral solution for the treatment of hypertension in pediatric patients 0 to 16 years of age on October 14, 2015. The Division was concerned that the prevalence estimates for pediatric hypertension provided in support of the designation were an underestimate and consulted the Division of Pediatric and Maternal Health (DPMH) regarding this issue. As discussed in Dr. Khurana’s consult, DPMH reviewed the sponsor’s amended estimates for the prevalence of pediatric hypertension and disagreed with the sponsor’s conclusion that the estimate of the prevalence is less than 200,000. According to Dr. Khurana, “Based on an independent review of available published and other publicly available data, DPMH’s calculated combined prevalence of primary pediatric hypertension (1,265,495) and secondary pediatric hypertension (590,304-927,309) exceed the maximum of 200,000 required for orphan designation. These estimates are based on 2014 U.S. census data and peer-reviewed published data that were available to the sponsor prior to their May 5, 2015 re-submission.”

On April 28, 2016, the Office of Orphan Products Development revoked orphan designation for lisinopril for the treatment of pediatric hypertension, noting that the prevalence of pediatric hypertension was in excess of the statutory threshold. On that same day, the applicant submitted a pediatric assessment for the treatment of hypertension. Because the submission was received a few days before the action date, the submission was deemed a major amendment, thus triggering an extension of the review clock.
Inspections and GCP: As previously noted: (1) the manufacturing facilities were found to be acceptable based on their inspectional histories and reviews during pre-approval inspections; (2) the data from the analytical site may be accepted without an on-site inspection because the site was recently inspected and classified as NAI; and (3) the inspection pertaining to the clinical portions of the submitted bioavailability studies (SG03-01 and SG03-02) did not identify any significant deficiencies.

12. Labeling

Proprietary name: The initially proposed proprietary name was considered unacceptable from a perspective. According to the DMEPA review, the proposed name was vulnerable to name confusion with The proposed proprietary name that was submitted in October 16, 2015, Qbrelis, was found to be acceptable.

Physician labeling: At this time, there are no outstanding issues related to physician labeling.

Carton and immediate container labels: According to DMEPA’s June 27, 2016 review, the revised container label and carton labeling submitted by the applicant on June 23, 2016 are unacceptable from a medication safety perspective. DMEPA’s review notes the presence of two barcodes on the container label which may lead to confusion; newly added storage information on the container label and carton labeling that is not present in the prescribing information; missing information on the dosage form on the top flap of the carton labeling, and information on the temperature range for storage on the carton label that is not consistent with the container label and PI. These issues have been communicated to the applicant.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
  Approval.

- Risk Benefit Assessment
  The application relies on the Agency’s previous finding of safety and effectiveness for the reference listed drug, Zestril® (lisinopril) tablets (NDA 019777, approved May 19, 1988), distributed by AstraZeneca Pharmaceuticals. Studies conducted in healthy subjects demonstrate bioequivalence of the oral solution and 10 mg Zestril® tablet in the fasted and fed state. From a CMC, non-clinical pharmacology-toxicology, clinical pharmacology and clinical safety and efficacy perspective, the application can be approved.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies
None.

- **Recommendation for other Postmarketing Requirements and Commitments**
  A deferred pediatric study under PREA in pediatric patients with hypertension who are 2 to < 6 years of age.

- **Recommended Comments to Applicant**
  None at this time.
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/s/

ALIZA M THOMPSON
07/17/2016