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APPLICATION NUMBER:

207078Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	May 17, 2018
From	Aliza Thompson
Subject	Cross-Discipline Team Leader Memo
NDA #	207078
Applicant	AstraZeneca Pharmaceuticals LP
Date of Submission	November 22, 2017
PDUFA Goal Date	May 22, 2018
Proprietary Name	Lokelma
Established or Proper Name	Sodium zirconium cyclosilicate
Dosage form(s)	Powder for Oral Suspension / 5 g and 10 g packets
Applicant Proposed Indication(s)/Population(s)	Treatment of hyperkalemia / Adults
Applicant Proposed Dosing Regimen(s)	Initial treatment: 10 g three times a day for up to 48 hours Maintenance treatment: 5 g daily with titration as needed up to 15 g daily
Recommendation on Regulatory Action	*Approval for the treatment of hyperkalemia in adults*

This secondary review is based on the following reviews:

Material Reviewed/Consulted	
Quality Assessment (4/16/2018)	Raymond Frankewich, Thomas Wong, Vidya Pai, and Mohan Sapru (Application Technical Lead)
Clinical Pharmacology Review (4/9/18)	Lars Johannesen and Sudharshan Hariharan
Clinical Reviews	Shen Xiao (5/16/18) Christine Garnett (5/11/18)
Division of Medication Error Prevention and Analysis Reviews	Sarah Thomas and Chi-Ming (Alice) Tu (2/6/18) Colleen Little and Chi-Ming (Alice) Tu (2/16/18)
Office of Prescription Drug Promotion Review (4/23/18)	Puja Shah
Division of Risk Management Review (5/1/18)	Mona Patel, Leah Hart, Jamie Wilkins

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Lokelma (sodium zirconium cyclosilicate) oral suspension is a potassium binder that captures potassium in exchange for hydrogen and sodium. On November 22, 2017, AstraZeneca Pharmaceuticals LP resubmitted NDA 207078 for sodium zirconium cyclosilicate oral suspension for the treatment of hyperkalemia. Previous submissions on May 26, 2015 and September 16, 2016 received Complete Response Letters for reasons other than efficacy.[1]

Hyperkalemia, often defined as a serum potassium > 5 mmol/L, is typically seen in patients with acute or chronic kidney disease or heart failure, particularly in those who are on medications that inhibit the renin-angiotensin-aldosterone system. Because marked elevations in serum potassium can cause fatal heart arrhythmias and abnormalities in conduction (progression of electrical impulses through the heart) and muscle weakness and paralysis (loss of muscle function), therapies are needed to treat hyperkalemia before life-threatening elevations occur.

The review team is in agreement that the application provides substantial evidence of sodium zirconium cyclosilicate's effectiveness in lowering serum potassium in patients with hyperkalemia and in maintaining control of potassium levels in patients who need continued therapy. Potential risks of the product include hypokalemia (low potassium) and edema (swelling caused by fluid in the tissue) resulting from absorption of sodium from the product. Data from the clinical development program indicate that these risks can be managed with appropriate patient monitoring. The submitted efficacy and safety data indicate that sodium zirconium cyclosilicate has a favorable benefit-risk profile for the treatment of hyperkalemia. Hence, I recommend approval.

[1] FDA issued a Complete Response (CR) Letter on May 26, 2016 citing deficiencies related to CMC issues (facility inspection findings and impurity levels), clinical pharmacology issues (drug-drug interaction liability), and outstanding labeling issues. ZS Pharma submitted a complete response to FDA's May 26, 2016 letter on September 16, 2016. Because of facility inspection findings, FDA issued a second CR Letter on March 16, 2017.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hyperkalemia, often defined as a serum potassium > 5 mmol/L, is typically seen in patients with acute or chronic kidney disease or heart failure, particularly in those who are on medications that inhibit the renin-angiotensin-aldosterone system. • Marked elevations in serum potassium levels can cause fatal heart arrhythmias and abnormalities in conduction (progression of electrical impulses through the heart) and muscle weakness and paralysis (loss of muscle function). The goal of therapy is to initiate treatments for hyperkalemia before life-threatening elevations occur.	Hyperkalemia can be a serious condition.
Current Treatment Options	• Patients who do not require an immediate reduction in potassium levels (i.e., those without life-threatening elevations) can be managed by dietary modifications, diuretics, medications that bind/capture potassium in the gastrointestinal tract, and by discontinuing medications that can case hyperkalemia. Because some medications that cause hyperkalemia reduce morbidity and mortality in patients with heart failure and/or kidney disease, discontinuing such medications in patients who develop hyperkalemia is not optimal. • Approved potassium binders (drugs that remove excess potassium from the body via binding/capturing potassium in the gastrointestinal tract) include sodium polystyrene sulfonate (SPS, Kayexalate), approved in 1958, and patiromer (Veltassa), approved in October 2015. Potential limitations of these agents include a relatively slow onset of action (both agents), poorly characterized efficacy (SPS), and safety concerns such as intestinal necrosis (SPS), the potential for drug-drug interactions with other orally administered medications (both agents), hypomagnesemia (patiromer and SPS)/other non-specific binding to cations (SPS), volume overload secondary to an increase in sodium load (SPS), hypokalemia (both agents) and gastrointestinal tolerability (both agents).	Treatment options exist for patients with hyperkalemia who do not require an immediate reduction in serum potassium levels (i.e., those without life-threatening elevations). Two drugs that bind/capture potassium in the gastrointestinal tract have been approved by the FDA for the treatment of hyperkalemia. Having additional agents with acceptable safety profiles would be advantageous.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Efficacy was demonstrated in two phase 3 trials, as well as a phase 2 trial. These trials demonstrated statistically significant and clinically relevant effects on serum potassium at the doses proposed for use in patients with hyperkalemia.	Lokelma (sodium zirconium cyclosilicate) is effective in lowering serum potassium in patients with hyperkalemia and in maintaining appropriate potassium levels in patients who require continued therapy for hyperkalemia.
Risk and Risk Management	• Risks of the product include edema (swelling caused by fluid in the tissue) resulting from absorption of sodium from the product. Each 5 g dose of Lokelma (sodium zirconium cyclosilicate) contains approximately 400 mg of sodium. Edema was more commonly seen in patients treated with 15 g once daily and tended to be mild to moderate in severity. • Risks also include hypokalemia (low potassium). In clinical trials, serum potassium levels were monitored and therapy was adjusted as needed. In these trials, approximately 4% of patients treated with Lokelma (sodium zirconium cyclosilicate) developed hypokalemia with a serum potassium value less than 3.5 mEq/L. Hypokalemia resolved with dosage reduction or discontinuation of Lokelma (sodium zirconium cyclosilicate). • Lokelma (sodium zirconium cyclosilicate) can change the absorption of oral medications whose solubility is dependent on pH (a measure of acidity or basicity). This could potentially lead to altered efficacy or safety of oral medications with pH dependent solubility that are taken close to the time that sodium zirconium cyclosilicate is taken.	Edema resulting from sodium absorption from the product is a risk, particularly at the highest dose recommended for extended use. This risk is expected to be mitigated/reduced with monitoring for edema. Patients who should restrict their sodium intake or are prone to fluid overload (e.g., patients with heart failure or kidney disease) are at greater risk. Labeling will include a Warning and Precaution about this risk. Among other things, the Warning and Precaution will instruct prescribers to (1) advise patients to adjust dietary sodium, if appropriate and (2) increase the dose of diuretics as needed. Hypokalemia (low potassium levels) is a potential risk of treatment. This risk is expected to be mitigated/reduced with appropriate monitoring of serum potassium levels and dose adjustments, as recommended in labeling. To reduce the risk of altering the efficacy or safety of other oral medications, labeling will indicate that oral medications should be taken at least 2 hours before or 2 hours after Lokelma (sodium zirconium cyclosilicate), unless it is known that absorption of the other medication is not affected by pH.

2. Background

Lokelma (sodium zirconium cyclosilicate) is a potassium binder that captures potassium in exchange for hydrogen and sodium. Through binding of potassium in the lumen of the gastrointestinal tract, sodium zirconium cyclosilicate increases fecal potassium excretion thereby lowering serum potassium levels. The proposed indication is for the treatment of hyperkalemia.

ZS Pharma Inc initially submitted NDA 207078 for sodium zirconium cyclosilicate for the treatment of hyperkalemia on May 26, 2015. As discussed in my memo dated May 20, 2016, the application provided substantial evidence of the product's effectiveness in lowering serum potassium in patients with hyperkalemia; however, because of deficiencies related to CMC issues (facility inspection findings and impurity levels), clinical pharmacology issues (drug-drug interaction liability), and outstanding labeling issues, FDA issued a Complete Response (CR) Letter on May 26, 2016. ZS Pharma submitted a complete response to FDA's May 2016 Action letter on September 16, 2016. Because of facility inspection findings, FDA issued a second CR Letter on March 16, 2017. At the time FDA issued the second CR letter, there were also outstanding labeling issues.

On November 22, 2017, AstraZeneca Pharmaceuticals LP (AstraZeneca) resubmitted NDA 207078 for Lokelma (sodium zirconium cyclosilicate) oral suspension. The submission contains information intended to address the quality/facility inspection deficiencies noted in FDA's CR letter dated March 16, 2017. The submission also contains the final clinical study report for Study ZS-005, an open-label maintenance study that was ongoing at the time of the prior review. Based on the findings in this study, the applicant proposed changes to dosing instructions and additional efficacy claims. The Clinical and OCP reviews focused on the findings in this study and the proposed labeling revisions.

3. Product Quality

OPQ recommends approval of the application from a quality perspective. According to their review, the quality issues, including the facility inspection-related deficiencies listed in the Complete Response Letter, dated March 16, 2017, have been satisfactorily resolved. There are no outstanding issues at this time and no phase 4 commitments are needed.

Drug Substance: Sodium zirconium cyclosilicate powder for oral suspension is an odorless, tasteless, free-flowing, insoluble, white crystalline powder. The chemical formula is $Na_{\sim 1.5}H_{\sim 0.5}ZrSi_3O_9 \bullet 2–3H_2O$.

Drug Product: The drug product consists of the drug substance (i.e., there are no inactive ingredients). Each 5 g of sodium zirconium cyclosilicate contains 400 mg of sodium. The drug product has a mean particle size of 20 µm, with no more than 3% of particles with a diameter below 3 µm. The drug product is packaged in (b) (4) foil pouch and comes in two strengths, 5 g and 10 g of sodium zirconium cyclosilicate. Prior to administration, the entire

contents of the packet(s) are emptied into a drinking glass containing approximately 3 tablespoons of water or more if desired. Patients stir well and then drink immediately.

Expiration Date and Storage Conditions: According to the Quality Assessment, the available stability data support the proposed expiry dating of (b) (4) months when packaged in the proposed packaging and stored under appropriate storage conditions 15°C-30°C (59°F-86°F).

Facilities review/inspection: A follow-up inspection was conducted at AstraZeneca Pharmaceuticals LP (previously ZS Pharma Inc.) in Coppell, TX to assess whether appropriate actions had been taken to address the previous inspectional observations at the site. According to the Quality Assessment, the corrective actions at the site, which manufactures the drug substance and conducts release and stability testing, are considered adequate. At this time, all facilities are acceptable.

4. Nonclinical Pharmacology/Toxicology

The application can be approved from a pharmacology/toxicology perspective. See Dr. Gatti's pharmacology/toxicology review dated January 8, 2016 and my memo dated May 20, 2016 for a discussion of key findings.

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) recommends approval of the application from a clinical pharmacology perspective. See the OCP reviews dated May 9, 2016 and January 27, 2107 and my memos dated May 20, 2016 and March 6, 2017 for discussion of the product's mechanism of action, general clinical pharmacology considerations, pathway of elimination, and drug-drug interaction liability.

In the current submission, the Applicant proposed to change the initial maintenance dose recommended in labeling from 10 (b) (4) g once a day (b) (4)

As discussed in the OCP review, the recommendation to use an initial maintenance dose of 10 g was based on analyses of data from Study ZS-004. In the first phase of Study ZS-004, all subjects were treated with 10 g three times daily for 48 to 72 hours; in the subsequent double-blind 28-day maintenance phase, subjects were randomized to placebo, 5, 10 or 15 g once a day of sodium zirconium cyclosilicate. As shown in Figure 1 of the OCP review, analyses of this trial indicated that for patients with baseline serum potassium concentrations greater than 5.5 mEq/L, a population of particular interest, ~74% of patients randomized to the 10 g maintenance dose achieved normokalemia as opposed to ~37% of patients randomized to the 5 g dose.

As in Study ZS-004, subjects in Study ZS-005 were initially treated with 10 g three times daily in the first phase of the trial; however, in the second phase of the trial, subjects were initiated on a maintenance dose of 5 g once daily, with further titration as needed based on serum potassium.

Analyses conducted by OCP indicate that an initial maintenance dose of 10 g is likely to result in fewer titration steps and that patients with hyperkalemia with higher baseline serum potassium levels (greater than 5.5 mEq/L) are likely to require higher doses than patients with lower baseline levels. Moreover, analyses of Study ZS-004 do not raise safety concerns with initiating maintenance therapy at the 10 g dose. Hence, OCP believes that labeling should recommend an initial maintenance dose of 10 g once daily. I think their rationale and recommendation are reasonable.

6. Clinical Microbiology

Sodium zirconium cyclosilicate is not an antimicrobial therapy.

7. Clinical/Statistical - Efficacy

As discussed in Dr. Xiao's clinical review dated April 7, 2016, Dr. Birkner's statistical review dated February 18, 2018, and my memo dated May 20, 2016, the initial application provided substantial evidence of sodium zirconium cyclosilicate's effectiveness in lowering serum potassium in patients with hyperkalemia, an accepted surrogate endpoint in this population, and in maintaining normokalemia in these patients.

The current submission contains the final clinical study report for Study ZS-005, an open-label, uncontrolled study in patients with hyperkalemia (serum potassium ≥ 5.1 mmol/L). The trial, as originally designed, included an open-label, uncontrolled phase and a randomized withdrawal phase (original protocol dated April 23, 2014). As discussed in Dr. Xiao's review, the randomized withdrawal phase of the trial was removed in a protocol amendment.

The stated primary objective of the trial was to obtain long-term (up to 12 months) safety and tolerability data for sodium zirconium cyclosilicate. Secondary objectives included evaluating efficacy during extended treatment. No formal sample size calculation was performed for the study, there was no control arm, and the protocol did not specify well-defined primary or secondary efficacy endpoints that would be tested within a plan that controlled the type-1 error rate.

As discussed in the clinical review, the data from the trial support the conclusion that efficacy is maintained during continued treatment, a conclusion that is also supported by the results of the open-label uncontrolled extension study to Study ZS-004.

8. Safety

Safety data from Study ZS-005 were reviewed by Dr. Xiao. Dr. Garnett also conducted analyses focused on risks of particular interest given the mechanism of action of the product and sodium counterion (i.e. hypokalemia, edema, heart failure, hypertension and weight gain).

- As would be expected given the patient population, adverse events of edema, heart failure and hypertension were reported. According to Dr. Garnett's analyses, the incidence of edema

(preferred terms of edema, peripheral edema and generalized edema) was 14%; while the incidence of heart failure (MedDRA HLT heart failure) was 5%. Adverse events of hypertension (SMQ Hypertension) were reported in 85 subjects (11%) during the extended dosing phase. There were no obvious changes in blood pressure or weight over time. Given the lack of a control arm, these data are difficult to interpret.

- There were no serious adverse events of hypokalemia in the trial. According to Dr. Garnett's review "There were 50 subjects with 1 (serum potassium) level <3.5mmol/L in the acute (n=1) or extended-dosing (n=49) phases and 9 subjects with 1 (serum potassium) level <3.0 mmol/L (all in extended dosing phase). None of the subjects had a (serum potassium) level below 2.5 mmol/L." These data indicate that with appropriate monitoring and dose adjustments, the risk of clinically significant hypokalemia should be manageable.

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

This application triggers PREA because the product is a new active ingredient. The applicant's proposal to conduct a deferred safety and pharmacodynamic study in pediatric patients with hyperkalemia 0 to 17 years of age was discussed with the PeRC on May 4, 2016 (initial submission) and March 8, 2017. On both occasions, the PeRC agreed with the Division's recommendation to grant a deferral in all pediatric patients because the product is ready for approval in adults. Given its mechanism of action, the product is expected to be effective in lowering serum potassium levels in pediatric patients with diminished renal potassium excretion; hence, from a FDA perspective, the study should be designed to provide needed data on safety, tolerability and dosing in children.

11. Other Relevant Regulatory Issues

None.

12. Labeling

Agreement has been reached with the applicant on labeling.

Prescribing Information

- In their resubmission, the applicant initially proposed to include a detailed discussion of post hoc efficacy analyses of trial Study ZS-005 including text discussing the proportion of patients who were able to continue, maintain the same dose, and initiate renin–angiotensin–aldosterone system inhibitor (RAASi) therapy during the trial. The proposed text on RAASi therapy seems misleading and promotional. Also, as previously noted, the

efficacy findings from this study are difficult to interpret because the trial did not include a control arm and did not have well-defined prespecified efficacy endpoints or a plan to control the overall type 1error rate in testing such endpoints. Missing data/subject attrition over the course of the trial also limit interpretation. Hence, the proposed text was removed and replaced with text indicating that the treatment effect on serum potassium was maintained during continued therapy in the trial.

- The label will include a Warning and Precaution instructing prescribers to avoid use in patients with gastrointestinal motility disorders (severe constipation, bowel obstruction or impaction) because the product has not been studied in patients with these conditions and may be ineffective and/or worsen gastrointestinal conditions. The label will also include a Warning and Precaution for edema, which will discuss the sodium content of the product, indicate that edema was more commonly seen at the highest dose (15 g once daily) and instruct prescribers to monitor for signs of edema, particularly in high risk populations (e.g., patients with heart failure and renal disease).

- The label will instruct prescribers to monitor serum potassium (Dosage and Administration) and provide information on the incidence of hypokalemia in clinical trials (Adverse Reactions). It will not contain a Warning and Precaution for hypokalemia because it was felt that, based on the findings in the development program (both incidence and severity of hypokalemia), a Warning and Precaution was not warranted. This issue should be revisited if cases of severe hypokalemia are seen in the post-marketing setting, when the product is used in a broader population in a less controlled environment.

Other Labeling

- Proprietary name: The proposed proprietary name, Lokelma, has been deemed acceptable by the Office of Medication Error Prevention and Risk Management.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

A REMS is not needed to ensure that the product's benefits outweigh its risks.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The applicant has agreed to conduct the following PREA PMR: A two-part study with an acute and maintenance phase to evaluate the safety, tolerability, and pharmacodynamic effects of Lokelma (sodium zirconium cyclosilicate) in pediatric patients 0 to 17 years of age with hyperkalemia. This study is also intended to satisfy EMA pediatric requirements.

14. Recommended Comments to the Applicant

None at this time.

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/s/

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05/17/2018

NORMAN L STOCKBRIDGE
05/18/2018

ELLIS F UNGER
05/18/2018
I fully agree with Drs. Thompson and Stockbridge.