CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207078Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type: NDA
Application Number: 207078
PDUFA Goal Date: May 22, 2018
OSE RCM #: 2017-2397
Reviewer Name(s): Mona Patel, PharmD, RAC
Team Leader: Leah Hart, PharmD
Deputy Director: Jamie Wilkins Parker, PharmD

Review Completion Date: May 1, 2018
Subject: Memorandum to File
Established Name: sodium zirconium cyclosilicate
Trade Name: Lokelma
Name of Applicant: AstraZeneca Pharmaceuticals LP
Therapeutic Class: Selective potassium trap
Formulation(s): Suspension
Dosing Regimen: Initial: 10 g three times daily for 48 hours
Maintenance: 10 g once daily, adjust dose in 5 g increments between 5
g every other day and 15 g daily
1 Introduction

This memorandum by the Division of Risk Management (DRISK) pertains to the New Drug Application (NDA) 207078 submitted on November 22, 2017 by AstraZeneca Pharmaceuticals LP and evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Lokelma (sodium zirconium cyclosilicate) is necessary to ensure the benefits outweigh its risks. AstraZeneca Pharmaceuticals LP resubmitted NDA 207078 for sodium zirconium cyclosilicate (SZC) with the proposed indication for the treatment of hyperkalemia after receiving a Complete Response (CR) letter on March 16, 2017, due to chemistry, manufacturing, and control (CMC) deficiencies.\footnote{DRISK completed a review on March 10, 2017, and concluded that based on the risk-benefit profile, a REMS was not necessary.} This application is under review in the Division of Cardiovascular and Renal Products (DCRP). The Sponsor did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION
Sodium zirconium cyclosilicate (SZC) is a cation exchanger which entraps potassium in the gastrointestinal tract in exchange for sodium and hydrogen, and is proposed for treatment of hyperkalemia.\footnote{Sodium zirconium cyclosilicate will be available as powder for oral suspension in 5 g and 10 g foil-lined packets and is likely to be prescribed by general practitioners and specialists. The applicant proposed an acute (3 times per day) and a chronic dosing (once daily) regimen. The recommended acute starting dose is 10 g administered three times a day for up to 48 hours. The recommended maintenance dose is 10 g once a day. The dose may be adjusted in 5 g increments between 5 g every other day and 15 g daily based on the serum potassium level.} Lokelma is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for NDA 207078 relevant to this review:

- 05/26/2015: NDA 207078 submission for the treatment of hyperkalemia received
- 05/26/2016: Complete Response letter sent to the applicant due to facility, clinical pharmacology, and product quality issues
- 09/16/2016: Resubmission received
- 03/16/2017: Complete Response letter sent to the applicant due to facility issues
- 11/22/2017: Resubmission received

\footnote{Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.}

\footnote{Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug}

\footnote{Draft Lokelma (sodium zirconium cyclosilicate) Prescribing Information, January 9, 2017}
3 Discussion of Need for a REMS

The risk associated with sodium zirconium cyclosilicate include edema. DRISK evaluated this risk in a review dated March 10, 2017, and determined at that time a REMS was not necessary to ensure the benefits of SZC outweigh the risks. At the time of this memorandum, the safety profile of SZC had not changed as there was no new safety information submitted to the application.

4 Conclusion and Recommendations

Based on the analysis in the DRISK review dated March 10, 2017 and no new safety information in the re-submission following the Complete Response letter, we maintain our determination that a REMS is not needed to ensure the benefits of SZC outweigh its risks.

Should DCRP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

5 Appendices

5.1 References


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/s/

MONA G PATEL
05/01/2018

JAMIE C WILKINS PARKER
05/01/2018
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Lokelma (sodium zirconium cyclosilicate [SZC]) is necessary to ensure the benefits of this product outweigh its risks. ZS Pharma Inc. submitted a New Drug Application (NDA 207078) for SZC with the proposed indication for the treatment of hyperkalemia. The risks associated with the use of SZC include the potential for drug-drug interactions and edema. The applicant did not submit a proposed REMS or risk management plan with this application.

It is the opinion of this reviewer that a REMS is not needed to ensure the benefits of taking (SZC) outweigh its potential risk of drug-drug interactions; this risk will be communicated through labeling.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Lokelma (sodium zirconium cyclosilicate [SZC]) is necessary to ensure the benefits of this product outweigh its risks. ZS Pharma Inc. submitted a New Drug Application with the proposed indication for the treatment of patients with hyperkalemia. This application is under review in the DCRP. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION
SZC is a cation exchanger which entraps potassium in the gastrointestinal tract in exchange for sodium and hydrogen, and is proposed for treatment of hyperkalemia. Other drugs in this class do not have a REMS, however the most recently approved cation exchanger, Veltassa (patiromer), did have a boxed warning regarding the potential for drug-drug interactions that was subsequently removed in 2016. Sodium zirconium cyclosilicate will be available as powder for oral suspension in 5 g and 10 g foil-lined packets and is likely to be prescribed by general practitioners and specialists. The applicant proposed an acute (3 times per day) and a chronic dosing (once daily) regimen. The recommended acute starting dose is 10 g administered three times a day for up to 48 hours. The recommended maintenance dose is 10 g, once a day. The dose may be titrated in 5 g increments between a minimum of 5 g every other day, and a maximum of 15 g once daily as needed to maintain serum potassium levels within the target range. Lokelma is not currently approved in any jurisdiction and is being reviewed under a standard review clock.

a Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

b Veltassa (patiromer) Prescribing Information, November 2016

c Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug

d Draft Lokelma (sodium zirconium cyclosilicate) Prescribing Information, January 9, 2017

Reference ID: 4067616
2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for NDA 207078 relevant to this review:

- **05/26/2015**: NDA 207078 submission for the treatment of hyperkalemia received
- **11/12/2015**: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data a REMS was not needed for SZC
- **03/23/2016**: Late-cycle Meeting
- **05/26/2016**: Complete Response (CR) letter sent to the applicant due to facility, clinical pharmacology, and product quality issues
- **09/16/2016**: Resubmission received

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION
Hyperkalemia is defined as serum potassium concentrations >5.5 mEq/L due to either excess total body stores or abnormal movement of potassium out of the cells. Contributing factors include increased dietary intake, medications that impair renal excretion, metabolic acidosis and acute or chronic kidney disease (CKD). Clinical manifestations include muscle weakness or paralysis, cardiac conduction abnormalities, and cardiac arrhythmias. If left untreated, hyperkalemia can lead to impaired nerve function, arrhythmias and cardiac arrest. Treatment depends on both the degree of hyperkalemia and severity of clinical manifestations and includes either removal of excess potassium from the body (cation-exchange resins, hemodialysis), or shifting potassium into cells (beta-adrenergic agonists, diuretics and insulin with dextrose). The prevalence of hyperkalemia in hospitalized patients is between 1 and 10 percent. The incidence of hyperkalemia is also increased in patients with heart failure or CKD (5% to 10%).

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS
Sodium polystyrene sulfonate (SPS), marketed under the tradename Kayexalate®, is a cation-exchange resin approved in the U.S. for the treatment of hyperkalemia. SPS was approved for treatment of hyperkalemia in June 1958. Intestinal necrosis, hypokalemia, electrolyte disturbances, and systemic alkalosis are listed as warnings for this drug. It is available as a suspension which can be administered orally or rectally and is dosed between one and four times a day, as needed.

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\(^{a}\) Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.


\(^{c}\) Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

Patiromer, marketed under the tradename Veltassa, is also a cation-exchange resin approved for the treatment of hyperkalemia. Patiromer was approved in 2015 as an oral suspension given once daily with food, supplied in single-use packets to be mixed with water. Due to the concern for binding drug-drug interactions, patiromer was initially approved with a boxed warning which stated that patiromer bound to many orally administered medications which could decrease their absorption and reduce their effectiveness, and that other oral medications were to be administered at least 6 hours before or 6 hours after patiromer. However, in 2016, the boxed warning was removed for this risk and labeling was written for patiromer to be administered at least 3 hours before or 3 hours after other oral medications. Patiromer also has a warning for worsening gastrointestinal motility and hypomagnesemia.

Other currently used treatments including insulin co-administered with dextrose, sodium bicarbonate, and inhaled β-adrenergic agonists are not approved by FDA for hyperkalemia and have several limitations, the most important being that the effect is transient and does not eliminate surplus potassium. However, these are the best practice for the management of hyperkalemia, especially in an emergent setting.

4 Benefit Assessment

The Applicant considered the efficacy of SZC to be supported by one phase 2 study (ZS-002) and two phase 3 studies (ZS-003 and ZS-004) for the treatment of hyperkalemia.

The phase 2 study, Z-002, was a multicenter, prospective, randomized, placebo-controlled, double-blind dose escalating study to investigate the safety, tolerability and pharmacodynamics of SZC in subjects with mild hyperkalemia (serum potassium between 5 and 6 mmol/L) in chronic kidney disease and moderate kidney dysfunction (GFR between 30 to 60 mL/min). SZC was administered orally, three times daily with meals for at least 48 hours or up to 96 hours in subjects whose serum potassium was not normalized after 48 hours. The primary endpoint was the difference in exponential rate of change in serum potassium levels during the initial 48 hours between SZC and placebo. Ninety patients were randomized and treated in 9 sites in the United States (US).

Study Z-003 was a phase 3, multicenter, two-phase, multi-dose, randomized, double-blind, placebo controlled study to investigate the safety and efficacy in subjects with mild to moderate hyperkalemia (serum potassium between 5.0 and 6.5 mmol/L). One of the 4 doses (1.25 g, 2.5 g, 5g and 10 g) of SZC was administered orally, three times a day for the acute phase for 48 hours followed by a randomized dose (1.25 g, 2.5 g, 5 g and 10 g) once daily in the subacute phase for 12 days. The primary endpoint was the difference in exponential rate of change in serum potassium levels during the initial 48 hours between SZC and placebo (a 5% relative reduction in serum potassium was deemed to be a minimally significant difference between treatment and placebo control over the first 48 hours).

Kayexalate (sodium polystyrene sulfonate)

At 65 sites in the US, Australia and South Africa, 753 subjects were treated in the acute phase and 543 were treated in the subacute phase. The exponential decrease in serum potassium during the acute phase was statistically significant for 2.5 g [p = 0.0315], 5 g [p = 0.0008], and 10 g [p < 0.0001] given three times daily when compared to placebo. In the subsequent subacute phase, the primary endpoint was statistically significant and superior to placebo for the 5 g [p = 0.0083] and 10 g [p < 0.0001] doses given once daily. This efficacy was consistent across subpopulations in subgroup analysis with no difference in efficacy based on demographic characteristics, baseline kidney function, baseline potassium level, concomitant diseases, and use of RAAS inhibitor medication.

Study Z-004 was a phase 3, multicenter, multi-phase, multi-dose, randomized, double-blind, placebo controlled study to investigate the safety and efficacy of SZC in subjects with hyperkalemia (serum potassium >5.1 mmol/L). SZC was administered three times daily for 48 hours during the acute phase, then once daily for 28 days during the maintenance phase. Subjects who developed serum potassium levels between 3.5 and 5 meq/L during the acute phase were treated with SZC every other day during the maintenance phase. The primary endpoint was the comparison of the mean serum potassium values over the period between days 8 to 29 in SZC and placebo treated patients.

At 44 sites in the US, Australia and South Africa, 251 subjects were treated during the acute phase and 237 of those were continued in the maintenance phase. All three doses (5 g, 10 g, and 15 g) of once daily SZC maintained mean potassium at lower levels than placebo (placebo average was 5.1 mEq/L vs. 4.8, 4.5, and 4.4 mEq/L for 5 g, 10 g, and 15 g, respectively, p-values≤0.001 for all doses. Statistically significant higher proportions of patients had mean serum potassium (K+) levels in the normal range (3.5 mEq/L-5.0 mEq/L) while on SZC than placebo. In both phase 3 studies, there were no limitations to the underlying etiology of hyperkalemia and the exclusion criteria were limited to evaluate patients who were likely to receive the drug in clinical practice. Overall, the results of both trials had statistically significant and clinically meaningful effects on serum potassium levels.

5 Risk Assessment & Safe-Use Conditions

The safety of SZC is based on analysis of safety and efficacy clinical trial data from 1760 patients with hyperkalemia. One of the drug-related adverse events (AE) identified in the clinical program which required treatment was an increase in the incidence of edema events, including general edema and peripheral edema in SZC treated patients. Additionally, drug-drug interactions are of clinical concern with SZC.

5.1 Edema

Based on the mechanism of action, edema is an expected adverse event, reported in 30/527 (5.7%) patients, and was more commonly seen in the 15 g versus 10 g dose.

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**Reference ID: 4067616**
Further analyses suggest that patients with comorbidities such as severe renal impairment, diabetes and heart failure as well as those patients taking a calcium channel blocker, may be susceptible to risk of edema and fluid overload. This adverse event was generally considered to be mild to moderate in severity; however, one subject in the clinical program developed pulmonary edema, which was considered to be a serious adverse reaction (SAR). Approximately half of the edema events resulted in treatment, typically with diuretics. Therefore, the risk of edema associated with SZC use will be communicated via labelling in the Warnings & Precautions section of the label as patients with comorbidities which make them more susceptible to the risk of edema and fluid overload may be treated with SZC.

5.2  **Drug-Drug Interaction**

During the clinical development program, an in vitro screening for drug interactions was completed to evaluate potential interaction between SZC and 39 orally administered compounds. These test compounds represented some of the commonly used concomitant medications in the target population. Of the 39 drugs that were screened, 22 drugs showed a positive interaction. The presence of SZC not only decreased drug concentrations but increased drug concentrations in some instances. There are clinically relevant interactions with SZC, as noted by an increase in C_{max} by ~65% for weakly acidic drugs such as atorvastatin and furosemide and a decrease in systemic exposure by ~40% for weakly basic drugs such as dabigatran.

Drugs with pH-dependent solubility that have not been studied could be impacted by co-administration with SZC. Based on the acid neutralizing properties of SZC, labeling will recommend 2 hour spacing with all concomitant drugs as prescribers are not likely to know which drugs have pH-dependent solubility, in the Drug Interactions section of the label.

At the time of this review, the label is still under review with the DCRP.

6  **Expected Postmarket Use**

SZC will be administered in the inpatient and outpatient setting and the likely prescribers will be general practitioners and specialists who are familiar with the risks and management of adverse events with this type of treatment based on a similar drug interaction profile for other known potassium binders such as that may be related to the drug and the background incidence of such events in the population likely to use the drug.

Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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\( n \) Lai, Ju Ping, Office of Clinical Pharmacology, Clinical Pharmacology Review for Lokelma (sodium zirconium cyclosilicate) January 27, 2017

\( p \) December 19, 2016 Clinical Pharmacology Mid-cycle Meeting Slides
SPS and patiromer. At the time of this review, no additional postmarketing studies are going to be required from the applicant.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for SZC beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of SZC on the basis of the efficacy and safety information currently available.

The efficacy data for SZC supports approval for the treatment of patients with hyperkalemia. The exponential decrease in serum potassium during the acute phase of Study Z-003 was statistically significant for 2.5g \( [p = 0.0315] \), 5 g \( [p < 0.0001] \) and 10 g \( [p < 0.0001] \) given three times daily when compared to placebo. In the subsequent subacute phase, this primary endpoint was statistically significant and superior to placebo for the 5 g \( [p = 0.0083] \) and 10 g \( [p < 0.0001] \) doses given once daily.

In Study Z-004, all three doses (5 g, 10 g, and 15 g) of once daily SZC maintained mean potassium at lower levels than placebo (placebo average was 5.1 mEq/L vs. 4.8, 4.5, and 4.4 mEq/L for 5 g, 10 g, and 15 g, respectively, p-value \( \leq 0.001 \) for all doses). Statistically significant higher proportions of patients had mean serum potassium (K+) levels in the normal range (3.5 mEq/L-5.0 mEq/L) while on SZC than placebo.

A risk of concern is the risk of drug-drug interactions. Although other current FDA-approved treatment options have a binding drug-drug interaction, the interaction with SZC is a pH dependent interaction. Based on in vivo drug-drug interaction studies and the acid neutralizing properties similar to antacid, at the time of this review, a 2-hour spacing with all concomitant drugs is going to be recommended in the Warnings and Precautions section of the label. Edema was also seen with SZC but not seen with other FDA-approved treatments for hyperkalemia. While the risk was generally not severe in nature, treatment was necessary for 50% of patients experiencing the AE, and comorbidities which would predispose a patient to experiencing edema are likely to occur in patients receiving SZC.

SZC will be administered in the inpatient and outpatient setting and the likely prescribers will be general practitioners and specialists who are familiar with the risks and management of adverse events associated with these types of treatments based on a similar drug interaction profile for other known potassium binders such as SPS and patiromer.

9 Conclusion & Recommendations

Based on the available data, if approved, this reviewer believes risk mitigation measures beyond professional labeling are not warranted for SZC for the proposed indication for treatment of hyperkalemia. The safety concerns associated with SZC will be addressed in labeling, and in general, healthcare providers who treat hyperkalemia will be familiar with these risks and how to mitigate them.
based on a similar drug interaction profile for other known potassium binders such as SPS and patiromer. Based on the risks associated with SZC in the clinical trials, a REMS is not necessary to ensure the benefits outweigh the risks.

Should the Division of Cardiovascular and Renal Products (DCRP) have any concerns or questions or if new safety information becomes available, please consult DRISK.

10 Materials Reviewed

The following is a list of materials informing this review:

a. Veltassa (patiromer) Prescribing Information, November 2016
b. Draft Lokelma (sodium zirconium cyclosilicate) Prescribing Information, January 10, 2017
c. Kayexalate (sodium polystyrene sulfonate)
d. Xiao, Shen, Division of Cardio-Renal Products, Clinical Review for Lokelma (sodium zirconium cyclosilicate) April 7, 2016
e. December 19, 2016 Clinical Pharmacology Mid-cycle Meeting Slides

11 Appendices

11.1 REFERENCES


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/s/

MONA G PATEL
03/09/2017

JAMIE C WILKINS PARKER
03/10/2017
Risk Evaluation and Mitigation Strategy (REMS) Deferral Memo

Date: May 23, 2016
Reviewer Leah Hart, PharmD,
Division of Risk Management (DRISK)
Team Leader Kimberly Lehrfeld, PharmD, DRISK
Division Director Cynthia LaCivita, PharmD, DRISK

Drug Name Lokelma™ (sodium zirconium cyclosilicate) powder for suspension
Therapeutic Class Potassium binder
Dosage and Route 5g, 10g, sodium zirconium cyclosilicate
Powder for oral suspension
Application NDA 207078
Type/Number
Applicant/ sponsor ZS Pharma, Inc.
OSE RCM # 2015-1554

*** This document contains proprietary and confidential information that should not be released to the public. ***
This memo is to defer Division of Risk Management (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Lokelma (sodium zirconium cyclosilicate), NDA 207087.

An application for the New Molecular Entity (NME) Lokelma was received by the Division of Cardiovascular and Renal Products (DCRP) from ZS Pharma Inc. (ZS Pharma) on May 26, 2015.

DCRP has determined that the submission currently under review will likely receive a CR based on inspection findings; therefore, DRISK defers comment on the evaluation of the need for a REMS for Lokelma (sodium zirconium cyclosilicate). Evaluation of the need for a REMS for Lokelma will be undertaken by DRISK after the Applicant resubmits the NDA for review.

This memo serves to close the existing consult request to DRISK for Lokelma (sodium zirconium cyclosilicate) under NDA 207078.

Reference ID: 3935366
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/s/
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LEAH M HART-BANKS
05/23/2016

KIMBERLY LEHRFELD
05/24/2016