CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207078Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207078

COMPLETE RESPONSE

ZS Pharma, Inc.
Attention: Adam Tomasi, PhD
Chief Scientific Officer
1100 Park Pl #300
San Mateo, CA 94403

Dear Dr. Tomasi:

Please refer to your New Drug Application (NDA) dated and received May 26, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LOKELMA (sodium zirconium cyclosilicate) powder for suspension, 5 gram and 10 gram packets.

We acknowledge receipt of your amendment dated September 16, 2016, which constituted a complete response to our May 26, 2016, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve the application in its present form. We describe our reasons for this action below and, where possible, provide suggestions for addressing these issues.

FACILITY INSPECTION

Failure to satisfy requirements of 505(a)(2)(B)

1. At the conclusion of the preapproval inspection of the drug substance manufacturing, release and stability testing facility (ZS Pharma Inc., Coppell, TX) on January 30, 2017, FDA Form 483 was issued. Your responses to this FDA Form 483 were reviewed and found to be inadequate. Unresolved FDA Form 483 issues concern your firm's capabilities to meet the requirements of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)]. Hence, the Office of Process and Facilities has issued a 'Withhold' recommendation for the facility. The application cannot be approved until all of the inspectional observations cited in FDA Form 483 concerning this facility are satisfactorily resolved.

PRESCRIBING INFORMATION

2. Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

    - The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
    - The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
    - Regulations and related guidance documents
    - A sample tool illustrating the format for Highlights and Contents
    - The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances, and
    - FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

    Submit draft labeling that addresses our proposed revisions in the attached labeling.

    Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

    To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

PROPRIETARY NAME

3. Please refer to our correspondence dated December 21, 2016, which addresses the proposed proprietary name, LOKELMA. This name was found to be acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
   - Present tabulations of the new safety data combined with the original application data.
   - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your

meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Draft Labeling

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ELLIS F UNGER
03/16/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207078

COMPLETE RESPONSE

ZS Pharma, Inc.
Attention: Jeffry Keyser, RPh, JD, PhD
Chief Operating Officer
508 Wrangler Drive
Suite 100
Coppell, TX 75019

Dear Dr. Keyser:

Please refer to your New Drug Application (NDA) dated and received May 26, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LOKELMA (sodium zirconium cyclosilicate) powder for suspension, 5 gram and 10 gram packets.

We also acknowledge receipt of your amendments dated March 4, 25, April 11, and May 19, 2016, which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application and have determined that we cannot approve the application at the present time. We describe our reasons for this action below and, where possible, provide suggestions for addressing these issues.

FACILITY INSPECTIONS

1. Objectionable conditions were identified during inspection of the drug substance manufacturing, release and stability testing facility (ZS Pharma Inc., Coppell, TX). Because of the inspection findings, the Office of Process and Facilities has issued a 'Withhold" recommendation for the facility. The application cannot be approved until all the inspectional observations cited in FDA Form 483 concerning this facility are satisfactorily resolved.

CLINICAL PHARMACOLOGY

2. The results of *in vitro* screening tests raise concern for a potential risk of drug interactions. Of the 39 drugs that were screened for interactions in an *in vitro* test system, nine exhibited a significant decrease in concentration (30% to 99%) in one or more media in the presence of sodium zirconium cyclosilicate, seven exhibited a significant increase in concentration or binding capacity (40% to 564%), and five exhibited inconsistent findings over different pH ranges in different media. Although many of these interactions appear to be the result of pH changes caused by sodium zirconium

cyclosilicate, there are drugs that showed concentration changes that cannot be explained solely by pH changes. On March 4, 25 and April 11, 2016, you submitted amendments to your application containing the results of *in vivo* drug-drug interaction studies for the following drugs: losartan, warfarin, atorvastatin, amlodipine and furosemide (March 4, 2016 amendment), levothyroxine and glipizide (March 25, 2016 amendment) clopidogrel and dabigatran (April 11, 2016 amendment). These *in vivo* study reports were submitted late in the review cycle; therefore, we have not completed our review of these amendments. Final study reports and associated data sets for the aforementioned *in vivo* drug-drug interaction studies must be submitted as part of your complete response, along with updated labeling.

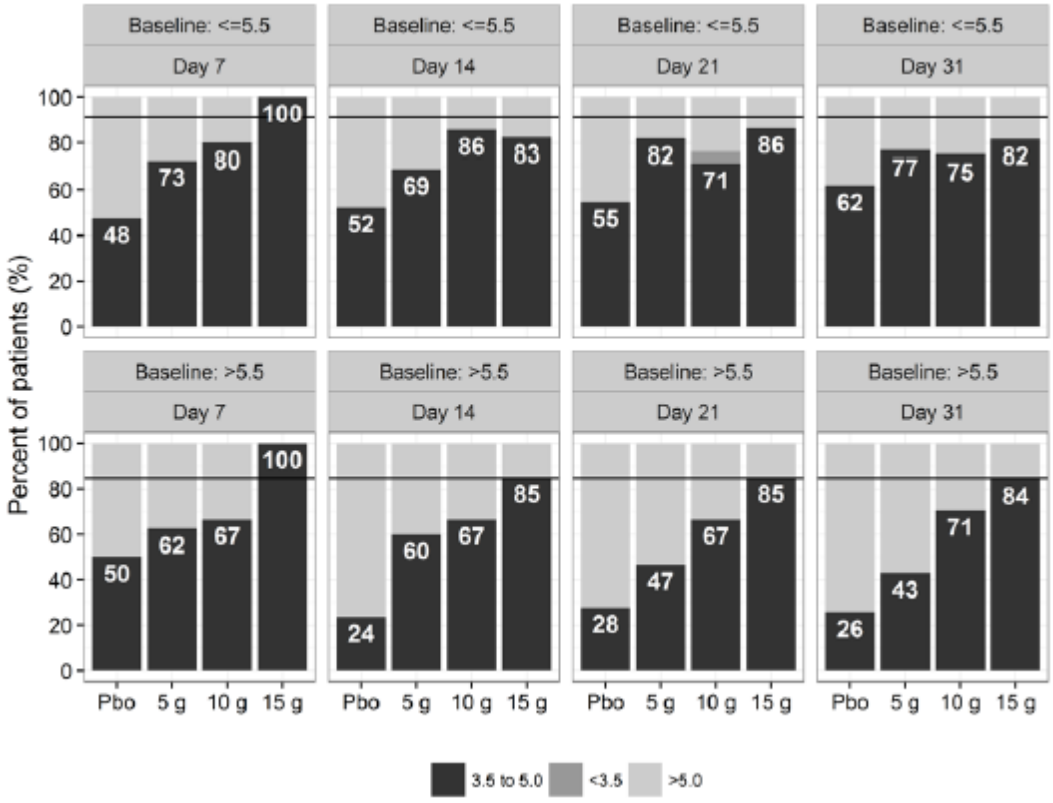
PRODUCT QUALITY

3. With a maximum daily dose of (b) (4) g, the maximum daily exposures of all specific elements are (b) (4) for each element. However, with a maximum daily dose of 15 g, which we are recommending, potential daily exposures (b) (4) for each of these elements. If we reach an agreement on a 15-g daily maintenance dose, then you will need to revise the acceptance criteria for these elemental impurities in order to comply with Q3D recommended PDE limits.

PRESCRIBING INFORMATION

4. On April 26, 2016, FDA sent proposed modifications to draft labeling for LOKELMA (sodium zirconium cyclosilicate) powder for suspension. On May 19, 2016, you submitted a response to FDA's proposed edits; in your response, you proposed further modifications to draft labeling, along with your rationale for the proposed modifications. As noted above, this amendment was not reviewed during the current review cycle. Your future resubmission should address the deficiencies and recommendations discussed in this letter as well as the modifications proposed by FDA in LOKELMA draft labeling dated April 26, 2016.

5. In your amendment dated March 15, 2016, you stated that you have decided to remove the reference to the 15 g dose from Section 2.1 of the Dosage and Administration Section of the Product Insert. Instead of recommending a maximum dose of 15 g once daily in Section 2.1, you are recommending a maximum dose of (b) (4) g once daily. Based on our review of the data, we believe a maximum daily dose of 15 once daily should be recommended in labeling. As shown in the figure below, among subjects with lower baseline potassium concentrations (i.e., ≤ 5.0 mmol/L), doses of 5, 10 and 15 g once daily appear to provide similar efficacy. In contrast, among patients with higher baseline serum potassium concentrations, there is a dose-dependent increase in the proportion of subjects achieving the target range of 3.5 – 5.0 mmol/L over a dose range of 5, 10 and 15 g once daily. Based on this analysis, it appears that some patients who are unable to achieve adequate control at 10 g once daily, will achieve control using the 15 g dose.



Percentage of patients achieving different serum potassium concentrations (3.5 to 5.0, < 3.5 and > 5 mmol/L) in the maintenance phase of Study ZS-004 by time and baseline serum potassium

Top panel: Patients with baseline serum potassium ≤ 5.5 mmol/L; Bottom panel: Patients with baseline serum potassium > 5.5 mmol/L. The solid and horizontal line represents the percentage of patients in the target range of 3.5 – 5.0 mmol/L at the end of the acute phase i.e., 10 g TID for 2 days).

6. As shown in the table below, edema/fluid overload, presumably resulting from absorption of sodium from the product, was observed at a higher frequency in the sodium zirconium

cyclosilicate groups compared to the placebo group in Study ZS-004, particularly at the highest dose evaluated for extended use (15 g once daily). Subgroup analyses suggest that patients with more severe renal impairment, those with diabetes and those with heart failure, as well as patients taking a calcium channel blocker, may be particularly susceptible to the risk of edema and fluid overload. There were also excess adverse events of heart failure/pulmonary edema in the sodium zirconium cyclosilicate group. Although the number of events was small, precipitation of heart failure is consistent with the drug's mechanism of action, and consistent with the findings of edema/fluid overload and weight gain. We believe a Warning and Precaution is warranted to address these findings.

MedDRA SMQ Haemodynamic oedema, effusions and fluid overload: Adverse events by treatment arm in Study ZS-004

MedDRA HLT and PT	Acute Phase Treatment 10 g ZS TID									
	Maintenance Phase Treatment									
	5 g ZS (N=45)		10 g ZS (N=51)		15 g ZS (N=56)		All Doses (N=152)		Placebo (N=85)	
	n	%	n	%	N	%	n	%	n	%
Total	***2***	**4.4**	**3**	**5.9**	**9**	**16.1**	**14**	**9.2**	**2**	**2.4**
Oedema NEC	1	2.2	3	5.9	8	14.3	12	7.9	2	2.4
Generalised oedema	0	0	0	0	2	3.6	2	1.3	0	0
Oedema	1	2.2	0	0	1	1.8	2	1.3	0	0
Oedema peripheral	0	0	3	5.9	6	10.7	9	5.9	2	2.4
Total fluid volume increased	1	2.2	0	0	1	1.8	2	1.3	0	0
Fluid overload	1	2.2	0	0	0	0	1	0.7	0	0
Fluid retention	0	0	0	0	1	1.8	1	0.7	0	0
Joint related signs and symptoms	0	0	0	0	1	1.8	1	0.7	0	0
Joint swelling	0	0	0	0	1	1.8	1	0.7	0	0

7. As previously communicated, the term [redacted] (b) (4) must be deleted from the product name in labeling since the term is not appropriate for the nomenclature of this product. The product name should read as follows: "Lokelma™ (sodium zirconium cyclosilicate) for oral suspension."

8. Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

   - The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
   - The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
   - Regulations and related guidance documents
   - A sample tool illustrating the format for Highlights and Contents, and
   - The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
   - FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

   Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

   To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

CARTON AND CONTAINER LABELING

9. Please submit draft carton and container labeling revised as follows:

   1) Container labels, carton labeling, and professional sample:

      A. Revise the strength statement "X g" to state "X g per packet" to make it clear that the designated strength is per unit.

      B. Replace the NDC number placeholder (0000-0000-00) to be consistent with the NDC number presented in the How Supplied/Storage and Handling section of the Prescribing Information.

      C. The term (b) (4) must be deleted from the product name in labeling since the term is not appropriate for the nomenclature of this product. The product name should read as follows: "Lokelma™ (sodium zirconium cyclosilicate) for oral suspension."

2) Container labels and carton labeling:

   A. Revise the container labels and carton labeling to include a barcode per 21CFR201.25. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the label whenever possible.

3) Container labels for 5 g and 10 g, and 10 g professional sample:

   A. Ensure a net quantity statement (e.g. "one packet") is displayed on the principal display panel of the container label in accordance with 21 CFR 201.51. Ensure the net quantity statement is placed away from the product strength so as to not cause confusion.

4) Carton labeling for 5 g, 10 g, and 10 g professional sample:

   A. As currently presented, the net quantity statement "contains XX packets" is located next to the strength. Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.

PROPRIETARY NAME

10. Please refer to correspondence dated, August 11, 2015, which addresses the proposed proprietary name, LOKELMA. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.

- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, please call Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research

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

/s/

ELLIS F UNGER
05/26/2016