Lokelma (Sodium Zirconium Cyclosilicate Powder for Suspension)  
NDA 207078  
Resubmission Review

Product Quality Recommendation: Not Recommended for Approval

<table>
<thead>
<tr>
<th>Drug Name/Dosage Form</th>
<th>LOKELMA (sodium zirconium cyclosilicate) powder for oral suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>5 g and 10 g packet</td>
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<tr>
<td>Route of Administration</td>
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</tr>
<tr>
<td>Rx/OTC Dispensed</td>
<td>Rx</td>
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<td>ZS Pharma Inc.</td>
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<td>Mohan Sapru</td>
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Submissions (s) Reviewed  
NDA 207078 resubmission, and all the submitted CMC amendments
EXECUTIVE SUMMARY

1. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) perspective, NDA 207078 is not recommended for approval because the Office of Process and Facilities has again issued a "withhold" recommendation for the drug substance manufacturing, release and stability testing facility i.e., ZS Pharma, Inc., Coppell, TX (FEI#3010199915).

2. Background and Quality Assessments

- On May 26, 2015, ZS Pharma Inc. submitted NDA 207078 to seek approval for Lokelma (Sodium Zirconium Cyclosilicate Powder for Suspension) for the treatment of hyperkalemia. On May 27, 2016, FDA issued a Complete Response Letter, in part, because the Office of Process and Facilities issued a "withhold" recommendation for the drug substance manufacturing, release and stability testing facility i.e., ZS Pharma, Inc., Coppell, TX. The "withhold" recommendation was issued due to unresolved FDA 483-related issues concerning this facility. Additionally, in order to use a maximum daily dose of 15 g, it was recommended that the applicant revise the acceptance criteria for elemental impurities to comply with Q3D recommended PDE limits.

- On September 16, 2016, ZS Pharma resubmitted NDA 207078 (Sodium Zirconium Cyclosilicate Powder for Suspension). In the resubmission, the applicant stated that all the identified FDA-483 issues have been addressed with corrective actions.

- Based on NDA 207078 resubmission, there is now agreement that the maximum recommended daily dose during continued treatment will be 15 g once daily, and the applicant has revised the acceptance criteria for elemental impurities to comply with the ICH Q3D recommended PDE limits.

- As a part of quality review of the resubmitted NDA, FDA investigators conducted a preapproval inspection (PAI) of drug substance manufacturing, release and stability testing site located at 508 Wrangler Drive, Suite 100; Coppell, Texas 75019 from January 18 – 30, 2017. At the conclusion of the preapproval inspection of the site, FDA issued FDA-483 on January 30, 2017. Outstanding concerns include, but are not limited to, the following:

  i) Failure to adequately qualify production equipment and validate production processes

  ii) Inadequate procedures for cleaning and maintaining processing equipment,
iii) Inadequately controlled manufacturing process.

The Agency received and reviewed ZS Pharma's response to FDA-483, dated February 10, 2017, and held a follow-up teleconference with the applicant on March 8, 2017. However, the Agency concluded that applicant's responses concerning specific violations of Section 501(a)(2)(B) of the act lack sufficient corrective actions, and hence remain unresolved.

3. OVERALL ASSESSMENT AND FINAL RECOMMENDATION

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing and controls (CMC) perspective, NDA 207078 is not recommended for approval because the Office of Process and Facilities has issued a ‘Withhold’ recommendation for the drug substance manufacturing, release and stability testing facility i.e., ZS Pharma, Inc., Coppell, TX (FEI#3010199915). The unresolved FDA-483 issues concern firm’s capabilities to meet the requirements of Section 501(a)(2)(B) of the Act for human drugs and commitments of the NDA. The application cannot be approved until all the inspectional observations cited in FDA-483 concerning this facility are satisfactorily resolved. Hence, the Office of Pharmaceutical Quality recommends issuing of Complete Response Letter to the applicant.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products (Acting)
ONDP/DNDPI/NDPBI

Attachment A: Life Cycle Knowledge Management
(Next page)

Final Risk Assessment: NDA 207078 (Sodium Zirconium Cyclosilicate)*
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<tr>
<th>Attribute/ CQA</th>
<th>Factors that can Impact the CQAs</th>
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<th>Risk Mitigation Approach</th>
<th>Final Evaluation</th>
<th>Lifecycle Considerations/ Comments</th>
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</table>
| Assay, Stability | • Formulation  
• Container closure  
• Impurity exceeding specification  
• Process parameters  
• Scale/equipment/site | Low (L) | Definitions of the active moiety and the drug substance are acceptable. Assay, and the levels of impurities are controlled by acceptable drug substance/product specifications | Acceptable | If in the future, the applicant proposes to include 15 g dosage strength, it would be necessary to revise the acceptance criteria for the Elemental Impurities i.e.,  
(9)(4) in order to comply with the Q3D recommended PDE limits |
| Physical stability (solid state) | • Formulation  
• Raw materials  
• Process parameters  
• Scale/equipment/site | Moderate (M) | Product stability has been demonstrated. The control strategy for controlling the levels is adequate | Acceptable | Future manufacturing changes should be evaluated for impact on content in the drug substance |
| Content uniformity and potassium exchange capacity (KEC) | • Formulation  
• Particle size  
• Segregation  
• Raw materials  
• Process parameters  
• Scale/equipment/site | Moderate (M) | Particle size, a CQA, is controlled by specification. The drug product is water-insoluble and not systematically absorbed. The product’s KEC, a measurement of the in-vitro activity of the product, is acceptable | Acceptable | Changes to formulation, manufacturing process, or product specification will need to be evaluated for impact on the identified product CQAs |
| Microbial limits | • Moisture  
• Process parameters  
• Scale/equipment/site | Low (L) | Typical microbial testing is performed on product release; the microbial recovery for total aerobic count has been validated per USP<61> and USP<1227>. | Acceptable | Changes to raw materials, formulation, manufacturing site, and process should be evaluated for impact on microbial contamination |
### QUALITY ASSESSMENT

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| Palatability       | • Formulation  
• Failure to mask unpleasant taste or smell  
• Excipient change                                                                 | Moderate (M)          | Because of input from the clinical review team, it was determined that based on experience from clinical trials involving adult subjects/patients, there were no palatability concerns regarding this formulation | Acceptable            | We may require that the applicant provide in-use stability data (12 - 24 hrs) to demonstrate stability of the product when administered with food (milk, baby food, yogurt etc). Given that the above-specified food items contain potassium, there is potential of potassium from the food items getting entrapped by Lokelma and, thereby, somewhat compromising the potassium binding/trapping ability of Lokelma prior to administration |
| Dosing accuracy    | • Formulation  
• Dosing Device  
• Process parameters  
• Scale/equipment/site | Moderate (M)          | No dosing accuracy-related concerns were identified during the NDA review.                | Acceptable            |  |

*The unacceptable product risk concerns the Form-483 cited deficiencies, which are unresolved and hence, CMC does not recommend approval for this NDA.*
QUALITY ASSESSMENT

REVIEW ADDENDUM WITH FINAL RECOMMENDATION: NDA 207078
(Sodium Zirconium Cyclosilicate)

RECOMMENDATION: NOT RECOMMENDED FOR APPROVAL

Note: This review addendum includes: a) final Executive Summary with recommendation on approvability, b) review of applicant’s responses to deficiencies that were pending at the time of completion of Integrated Quality Review as per the GRMP date (for review details, refer to OPQ Integrated Quality Assessment – NDA 207078 document in Panorama), and c) list of unresolved deficiencies.

Final Executive Summary

Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) perspective, NDA 207078 is not recommended for approval because the Office of Process and Facilities has issued a ‘Withhold’ recommendation for the drug substance manufacturing, release and stability testing facility i.e., ZS Pharma, Inc., Coppell, TX (FEI#3010199915).

I. Summary of Quality Assessments

The applicant, ZS Pharma Inc., has sought marketing approval for sodium zirconium cyclosilicate for oral suspension under the provisions of Section 505(b)(1). Sodium zirconium cyclosilicate powder for oral suspension is a non-absorbed, insoluble, free-flowing, odorless, tasteless white crystalline powder. It is an inorganic cation exchange agent with a high capacity to selectively entrap monovalent cations, specifically potassium and ammonium ions, but not divalent cations like calcium and magnesium, as it traverses the GI tract. This non-sterile solid oral dosage formulation has been developed for the treatment of hyperkalemia.

A) Drug Substance Quality Summary

The applicant has classified the drug substance, sodium zirconium cyclosilicate, as a New Molecular Entity (NME). The applicant contends that sodium zirconium cyclosilicate is not an ester or salt of zirconium oxide, and is not a non-covalent derivative (such as complex, chelate, or clathrate) of zirconium oxide. The applicant has carried out a structural characterization of the drug substance using standard powder diffraction as well as synchrotron powder diffraction approaches. Based on powder X-ray diffraction patterns (PXRD) comparison, the fingerprint of sodium zirconium cyclosilicate appears different than any of the three reported ZrO2 structures. Additionally, the peaks of the zirconium oxides are not present in the signature pattern of sodium zirconium cyclosilicate. Specifically, the three dimensional microporous framework structure of sodium zirconium cyclosilicate consists of corner sharing zirconium-oxygen octahedra and silicon-oxygen tetrahedra resulting in a unique cubic structure with a distinct set of physico-chemical attributes. Bonding
interactions in the main framework are considered primarily of covalent nature, with some ionic contribution due to the difference in electronegativity between Si–O and Zr–O. The applicant has provided evidence that suggests that zirconium–oxygen and silicon–oxygen bonding meet the criteria of covalency. The applicant contends that since the geometrical features of the zirconium cyclosilicate structure meet the criteria of covalency in the Si–O–Zr and Si–O–Si bond extended fractions, i.e., directionality, and the structure is stable at relatively high temperatures (~300°C), the main structure can be declared a “covalent framework”. The framework acquires its negative charge from the octahedral fractions, [ZrO6]2–, and features channels and cavities that interconnect and house the positive ions that counter-balance the negative charge of the framework. Electrostatic interactions between the framework and the cations allow for mobility and possibility of exchange for other cations that would fit and pass the free pore openings of ~ 3.0 Å, providing the compound with its distinctive ion-exchange selectivity features.

The framework featuring channels and cavities that interconnect and house the positive ions to counter-balance the negative charge of the framework i.e., Na~1.5H~0.5ZrSi3O9 • nH2O (n' = 2–3) constitutes the drug substance. Interstitial, or lattice water despite not being connected through covalent bonds to the framework, plays the very important role of stabilizing the structure from collapse. The applicant proposes that the active moiety is the negatively charged framework. Although water is considered an essential part of what the applicant describes as the covalent framework, it cannot be considered part of the active moiety because it is not bonded in a covalent manner to the framework. Therefore, we consider the Si–O–Zr and Si–O–Si is supported by the following criteria:

- The bonds are directional.
- The structure (SZS) is thermally stable.
- The SZS structure is not water-soluble and does not undergo swelling or expansion when saturated with water.

The above-listed characteristics, in addition to apparent stability at gastric and biological pH environments (in particular the ones involving Simulated Gastric Fluid) indicate that SZS is capable of traversing the body without being structurally changed. Viewed in this context, SZS could be regarded as a stable compound that performs its intended function while maintaining its structural integrity. Importantly, sodium would not be considered to be covalently bonded in any manner to the ZrO6 / SiO4 framework, or to any other entity. This is demonstrated by the randomness of the Na ions in the dry structure, and the fact that the relationship between Na and the framework can be changed by water diffusing through the channels. In addition, Na–O bonds that exist appear to be variable in distance and longer than Si–O and Zr–O bonds.

Manufacturing: The sodium zirconium cyclosilicate (ZS), an ordered extended microporous tri-dimensional (3D) compound, is manufactured and the manufacturing process is adequately controlled.
**Control Strategy:** The release specification includes tests for drug substance CQAs such as identity, purity, potassium exchange capacity, particle size, impurity profiles, including testing for the elemental impurities. All the non-compendial analytical methods have been adequately validated for critical analytical parameters, and are suitable for intended applications. The drug substance specification is one part of the overall control strategy, which also includes suitable in-process controls for the manufacturing process.

**Container Closure System:** The drug substance is stored. Regarding this submission, there is no difference between the drug substance and drug product, and the packaging used for the drug product is well-defined and acceptable.

**Retest Period and Storage Conditions:** Primary and supportive stability studies support a retest period of months for the drug substance when stored. The proposed retest period is based on real-time stability data through months storage for three batches, which were manufactured using the process proposed for commercial use, but at a scale of L (proposed commercial scale of L).

**B) Drug Product Quality Summary**

Sodium zirconium cyclosilicate powder for oral suspension is a non-absorbed, white crystalline mixable powder with a specific particle size distribution profile > 3 μm and no inactive ingredients. This product will be packaged in foil pouch to produce two strengths, 5 g and 10 g of sodium zirconium cyclosilicate. Regarding the product use, the patients will be instructed to empty entire packet into a drinking water with about 3 tablespoons (1.5 ounces) of water or more if desired, stir well and drink the suspension immediately.

**Product Design:** the quality target product profile (QTPP) and critical quality attributes (CQA) of the finished product are. The potassium exchange capacity (KEC) is a measure of the ability of the drug product to bind potassium in solution, and is effectively a measurement of the in-vitro activity of the product. The added advantage of selecting this drug substance, with efficient potassium exchange capacity, for product development is because of its water insolubility and its systemic non-absorbability. The acceptance limits for sodium have been set at 6%

**Manufacturing:** Given that the drug product comprises entirely of drug substance, the drug product manufacturing consists of. Because very fine particles can lead to systemic absorption of sodium zirconium cyclosilicate, the limit for fines (volume < 3 micron: NMT 3%) as reported by Particle Size Determination has been established based on a safety consideration from preclinical data.

**Microbiological Aspects:** Regarding the microbial aspects, bioburden tests and water activity testing on drug substance and product lots show that the extreme process conditions (high temperature, pressure, low pH) results in a low microbial load. Regarding microbial testing, the microbial recovery for total aerobic count has been validated per USP<61> and USP<1227>.
Biopharmaceutics Aspects: Regarding the biopharmaceutics aspects, the proposed drug product, which is insoluble in acidic, neutral, and basic media, is not systemically absorbed following oral administration. In vitro dissolution testing for routine QC of the proposed drug product is not necessary. Since Lokelma is indicated for the treatment of hyperkalemia, the ability of sodium zirconium cyclosilicate to absorb potassium ions (K+) is a critical quality attribute of the drug product. Based on adequate method validation data, including the degradation studies, the proposed Potassium Exchange Capacity (KEC) is acceptable as a routine QC test for batch release and stability testing of SZS powder for oral suspension. Based on the characteristics of the clinical trial lots used in the Phase 3 trials (ZS-003 and ZS-004), the proposed acceptance criterion (i.e., mEq/g) for Potassium Exchange Capacity (KEC) is acceptable.

Control Strategy: The product control strategy mainly consists of in-process controls, and release testing have been included as part of in-process controls. The release specification includes tests for the entire identified drug product CQAs, including the particle size determination. There is no organic impurity present in the drug product. The only inorganic impurities present in the drug product are introduced as elemental impurities. These elemental impurities are identified and quantified.

Container Closure System: The primary package for sodium zirconium cyclosilicate isTrade sizes of 5 g and 10 g pouches will be placed into a carton.

Expiration Date & Storage Conditions: The proposed product shelf-life of months, when packaged in foil pouches and stored is supported by the primary and supporting stability data. Specifically, the month expiry dating has been determined based on the available 12-month long-term stability data and 6-month accelerated stability data on batches packaged in foil pouches in compliance with the ICH Q1E guidance.

C. Summary of Drug Product Intended Use

<table>
<thead>
<tr>
<th>Proprietary Name of the Drug Product</th>
<th>LOKELMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Proprietary Name of the Drug Product</td>
<td>Sodium zirconium cyclosilicate for oral suspension</td>
</tr>
<tr>
<td>Non-Proprietary Name of the Drug Substance</td>
<td>Sodium zirconium cyclosilicate</td>
</tr>
<tr>
<td>Proposed Indication(s) including Intended Patient Population</td>
<td>LOKELMA™ (sodium zirconium cyclosilicate) for oral suspension is indicated for the treatment of hyperkalemia</td>
</tr>
<tr>
<td>Methods of Administration</td>
<td>Oral suspension</td>
</tr>
</tbody>
</table>
D. Biopharmaceutics Considerations

Not applicable because the drug product is insoluble and not absorbed.

- Drug Substance: N/A
- Drug Product: N/A

Biowaivers (BA) / Biostudies:

The applicant’s biowaver request is not needed because in vivo BA studies in dogs and humans have been conducted; and there is no evidence of systemic absorption following oral administration.

- PK studies: Refer to the Clinical Pharmacology review.
- IVIVC: Not applicable.

II. List of Unresolved Deficiencies:

1. **Facility**: Based on pre-approval inspection, the Office of Process and Facilities has issued a “Withhold” recommendation for the drug substance manufacturing, release and stability testing facility i.e., ZS Pharma, Inc., Coppell, TX. Satisfactory resolution of all the inspectional observations cited in FDA-483 concerning this facility is required before this NDA can be considered for approval.

2. **Labeling**: During the review period, the applicant was advised to delete the term [REDACTED] from the product name since the term is not appropriate for the nomenclature of this product. Though the applicant agreed to do so (per NDA 207078 Seq. 0026, dated April 8, 2016), however, the container labels have not been changed. We recommend using the following product name for appropriate labeling:

   Lokelma™ (sodium zirconium cyclosilicate) for oral suspension.

3. **Elemental Impurities Specification**: With a maximum daily dose of [REDACTED] g, the maximum daily exposures of all specific elements are [REDACTED] for each element. However, if the maximum daily dose is changed to 15 g, potential daily exposures to some of the elements [REDACTED] would be [REDACTED] for these elements. Therefore, if in the future the applicant proposes to include 15 g dosage strength, it would be necessary to revise the acceptance criteria for the
Elemental Impurities in order to comply with Q3D recommended PDE limits.

III. Life Cycle Knowledge Information:

See Final Risk Assessment on page Attachment A.

OVERALL ASSESSMENT AND RECOMMENDATION

From the chemistry, manufacturing and controls (CMC) perspective, NDA 207078 is not recommended for approval because the Office of Process and Facilities has issued a ‘Withhold’ recommendation for the drug substance manufacturing, release and stability testing facility i.e., ZS Pharma, Inc., Coppell, TX (FEI#3010199915).

Specifically, at the time of NDA submission, the applicant notified the Agency that all the manufacturing and testing facilities are ready for inspection. However, upon pre-approval inspection of the ZS Pharma, Inc., Coppell, TX facility during the review period, the Agency investigators learnt that the facility was not inspection-ready.

At the conclusion of the recent pre-approval inspection of the ZS Pharma, Inc., Coppell, TX facility (conducted from March 17-29, 2016), FDA investigators issued FDA-483, dated March 29, 2016. ZS Pharma’s responses to FDA-483 were found to be inadequate. Based on recommendations from Dallas District, Office of Process and Facilities has issued a ‘Withhold’ recommendation for the ZS Pharma, Inc., Coppell, TX facility. Hence, from CMC perspective, NDA 207078 is not recommended for approval. For any future resubmission, the applicant will need to address all the unresolved deficiencies that have been listed above in the Executive Summary.

Mohan Sapru, Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products (Acting)
Application Technical Lead (ATL) Signature

May 10, 2016
VI. LABELING AND PACKAGE INSERT ASSESSMENT

During a labeling meeting, the Nomenclature and Labeling Committee has recommended to delete the term (n) from labeling so that the revised label states: “Sodium Zirconium Cyclosilicate for Oral Suspension”.

The following comment was sent to the applicant:

During labeling review, the Nomenclature and Labeling Committee recommended that the term (n) be deleted from the proposed name of the drug product. The recommended drug product name should be: Sodium Zirconium Cyclosilicate for Oral Suspension. Please revise the name of the product in the Package Insert and the container labels accordingly.

The applicant responded on April 8 that they will revise the name of the drug product according to the Agency’s recommendation.

Reviewer’s Assessment: Acceptable.

The response is acceptable.

OVERALL ASSESSMENT AND SIGNATURES: PRODUCT LABELING

Reviewer’s Overall Assessment and Signature:

Adequate. There is no pending issue for the drug product labeling.

Thomas Wong, Ph.D., ONDP/Division of New Drug Products I/Branch I

Secondary Review Comments and Concurrence: I concur.

Wendy I. Wilson-Lee, Ph.D.
Branch Chief (Acting), Branch 1
DNDP1/ONDP
## Attachment A: Life Cycle Knowledge Management

### Final Risk Assessment: NDA 207078 (Sodium Zirconium Cyclosilicate)*

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| Assay, Stability | • Formulation  
• Container closure  
• Impurity exceeding specification  
• Process parameters  
• Scale/equipment/site | Low (L) | Definitions of the active moiety and the drug substance are acceptable. Assay, and the levels of impurities are controlled by acceptable drug substance/product specifications | Acceptable | If in the future, the applicant proposes to include 15 g dosage strength, it would be necessary to revise the acceptance criteria for the Elemental Impurities i.e., in order to comply with the Q3D recommended PDE limits |
| Physical stability (solid state) | • Formulation  
• Raw materials  
• Process parameters  
• Scale/equipment/site | Moderate (M) | Product stability has been demonstrated. The control strategy for controlling the levels is adequate | Acceptable | Future manufacturing changes should be evaluated for impact on content in the drug substance |
| Content uniformity and potassium exchange capacity (KEC) | • Formulation  
• Particle size  
• Segregation  
• Raw materials  
• Process parameters  
• Scale/equipment/site | Moderate (M) | Particle size, a CQA, is controlled by specification. The drug product is water-insoluble and not systemically absorbed. The product’s KEC, a measurement of the in-vitro activity of the product, is acceptable | Acceptable | Changes to formulation, manufacturing process, or product specification will need to be evaluated for impact on the identified product CQAs |
| Microbial limits | • Moisture  
• Process parameters  
• Scale/equipment/site | Low (L) | Typical microbial testing is performed on product release; the microbial recovery for total aerobic count has been validated per USP<61> and USP<1227>. | Acceptable | Changes to raw materials, formulation, manufacturing site, and process should be evaluated for impact on microbial contamination |
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<td>Palatability</td>
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<td>Moderate (M)</td>
<td>Because of input from the clinical review team, it was determined that based on experience from clinical trials involving adult subjects/patients, there were no palatability concerns regarding this formulation</td>
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<td>May require that the applicant provide in-use stability data (12 - 24 hrs) to demonstrate stability of the product when administered with food (milk, baby food, yogurt etc). Given that the above-specified food items contain potassium, there is potential of potassium from the food items getting entrapped by Lokelma and, thereby, somewhat compromising the potassium binding/trapping ability of Lokelma prior to administration</td>
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<td>Dosing accuracy</td>
<td>• Formulation&lt;br&gt;• Dosing Device&lt;br&gt;• Process parameters&lt;br&gt;• Scale/equipment/site</td>
<td>Moderate (M)</td>
<td>No dosing accuracy-related concerns were identified during the NDA review.</td>
<td>Acceptable</td>
<td></td>
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*The unacceptable product risk concerns the Form-483 cited deficiencies, which are unresolved and hence, CMC does not recommend approval for this NDA.*
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRIAN L PROCTOR
05/22/2018
NDA 207078 Resubmission

Lokelma (Sodium Zirconium Cyclosilicate) for Oral Suspension

Integrated Quality Review of NDA 207078; 2nd Resubmission; 3rd Review Cycle)

Product Quality Recommendation: Recommended for Approval

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Submission(s) Reviewed          | NDA 207078 NDA Resubmission (3rd review cycle), and all the amendments |
EXECUTIVE SUMMARY

I. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC) perspective, NDA 207078 (2nd resubmission; 3rd review cycle) is recommended for approval. All the quality deficiencies, including the facility inspection-related deficiencies listed in the Complete Response Letter, dated 16 March 2017, have been satisfactorily addressed by the applicant.

2. Background Summary

The applicant AstraZeneca Pharmaceuticals (previously ZS Pharma Inc.) has resubmitted NDA 207078 (2nd resubmission; 3rd review cycle) to seek marketing approval for Lokelma (Sodium Zirconium Cyclosilicate) for Oral Suspension. The drug substance, sodium zirconium cyclosilicate, has been classified as a New Molecular Entity (NME). Updated CMC data to address the quality deficiencies, including drug substance manufacturing facility-related issues have been addressed per the amendments made to Module 3 of this NDA resubmission.

3. Summary of Quality Assessment

Module 3 has been updated to include information and data that demonstrate that all critical processing parameters have been identified and controls established to ensure that critical quality attributes (CQAs) are consistently controlled within established specifications. An understanding of process parameters affecting these CQAs has been obtained based on revised manufacturing process development studies and manufacturing experience at the proposed commercial scale. The potassium exchange capacity (KEC) is effectively a measurement of the in-vitro activity of the product. The applicant’s recent studies support that KEC, a CQA is not scale-dependent. The updated batch analyses data further demonstrate that drug substance process is well-controlled. Based on Agency feedback via the FDA Meeting Preliminary Comments (Reference ID 4095898, dated 09 May 2017, a response to a meeting request, dated 17 April 2017), the maximum specification limit for potassium exchange capacity (KEC) was increased to 000 mEq/g. In accordance with the process controls detailed in the resubmission, successful validation of sodium zirconium cyclosilicate to the proposed specifications has been accomplished and the report is provided within Module 3, Section S.2.5 Process validation and/or evaluation for drug substance. For detailed integrated quality reviews, please refer to Panorama documents i.e., OPQ Integrated Quality Assessment and Final Recommendation (dated 2/3/2016 and 5/10/2016) for the original NDA submission, and Integrated Quality Assessment (dated 3/14/2017) for the 1st resubmission. This current Integrated Quality Assessment captures in detail quality
review of applicant's CMC information and data, including correctional action taken to address drug substance manufacturing facility-related FDA 483 deficiencies.

3.1. Drug Substance

A) Sodium Zirconium Cyclosilicate (ZS): ZS powder for oral suspension is a non-absorbed, insoluble, free-flowing, odorless, tasteless white crystalline powder. It is an inorganic cation exchange agent with a high capacity to selectively entrap monovalent cations, specifically potassium and ammonium ions but not divalent cations like calcium and magnesium, as it traverses the GI tract. The drug substance process development described in the resubmission adequately supports the proposed commercial-scale synthetic scheme, manufacturing process, and control strategy. The updated details concerning identified critical process parameters (CPPs) and controls of critical steps and intermediates have been provided. The rationale for critical process parameters and controls as well as the acceptance ranges (where applicable) is adequate. The revised acceptance limit of \(0^0\text{mEq/g}\) for KEC is acceptable. The KEC data for the six (6) validation batches demonstrate that drug substance produced using the validated process consistently meets the revised KEC acceptance limits. In summary, the drug substance manufacturing process is well controlled and proposed drug substance specification is adequate to ensure the quality of the drug substance as it relates to the safety and efficacy of the eventual drug product.

B) Retest Period: The proposed retest period of \(0^0\text{months}\) is justified based on applicant's stability data for the drug substance.

3.2. Drug Product

A) Product Design: Sodium zirconium cyclosilicate (ZS) powder for oral suspension is a non-absorbed, white crystalline mixable powder with no inactive ingredients. It has a mean particle size of 20 \(\mu\text{m}\) and includes no more than 3% of particles with a diameter below 3 \(\mu\text{m}\). Each 5 g of sodium zirconium cyclosilicate contains 400 mg of sodium. Lokelma increases fecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract. Binding of potassium reduces the concentration of free potassium in the gastrointestinal lumen, thereby lowering serum potassium levels. The quality target product profile (QTPP) and critical quality attributes (CQA) of the finished product are a measure of the ability of the drug product to bind potassium in solution, and is effectively a measurement of the in-vitro activity of the product. The added advantage of selecting this drug substance, with efficient potassium exchange capacity, for product development is because of its water insolubility and its systemic non-absorbability. The product is to be packaged in \(0^0\text{foil pouch}\) to produce two strengths, 5 g and 10 g of sodium zirconium cyclosilicate. Regarding the product use, the patients will be instructed to empty entire packet into a drinking water with about 3 tablespoons (1.5 ounces) of water or more if desired, stir well and drink the suspension immediately.
B) **Drug Product Manufacturing:** Given that the drug product comprises entirely of drug substance, the drug product manufacturing simply consists of

Because very fine particles can lead to systemic absorption of sodium zirconium cyclosilicate, the limit for fines (volume < 3 micron: NMT 3%) has been established based on a safety consideration from preclinical data. Batches manufactured with this target have demonstrated consistent delivery of labeled content. Process validation will be completed prior to commercial distribution of the product. The revised KEC acceptance is supported by the stability data (ranged from \( 0 \text{ mEq/g at long-term storage conditions} \)). Regarding revised drug product specification, the removal of the test and the contents are acceptable because testing for these attributes is included in the drug substance specification. Regarding the proposed FTIR identity test method for the drug product, the applicant contends that it fulfills the requirements of ICH Q6A, which requires the test method to be able to discriminate between compounds of closely related structure, which are likely to be present. Although the drug substance manufacturing process and specification for ZS Viewed, in light of extensive structural characterization of the drug substance and demonstrated high degree of specificity of method for confirming the identity against ZS reference material, the applicant’s approach is acceptable.

C) **Assessment of Manufacturing Facilities:** The most recent inspection was intended to follow-up on adequacy of the firm’s corrective actions to the previous inspectional observations. The field recommendation indicated that the inspection concluded with no FDA 483 citations. DAL-DO recommended approval for the facility. All the quality deficiencies, listed in previously issued Complete Response (CR) letter, including the drug substance manufacturing facility-related issues, have been resolved. The office of Process and Facilities has recommended overall approval for all the currently listed manufacturing facilities concerning this NDA.

4. **Expiration Date & Storage Conditions:** The proposed product shelf-life of \( 0 \) months, when packaged in foil pouches and stored at 15°C-30°C (59°F-86°F), is supported by the primary and supporting product stability data.

5. **Environmental Assessment:** The applicant via Amendment Seq. # 0045 submitted a claim for categorical exclusion in accordance with 21 CFR 25.31 (a). Per this amendment, to the best of the sponsor’s knowledge, no extraordinary circumstances, as referenced in 21 CFR 25.21, exist relative to this action. The claim for categorical exclusion is acceptable.

6. **Novel Approaches:** The novel NME drug substance, sodium zirconium cyclosilicate, belongs to the family of ordered extended microporous tri-dimensional (3D) compounds, which are manufactured
7. OVERALL ASSESSMENT AND FINAL RECOMMENDATION

Application Technical Lead (ATL) Assessment and Signature

From the chemistry, manufacturing, and controls (CMC) perspective, NDA 207078 (2nd resubmission; 3rd review cycle) is recommended for approval. All the quality deficiencies, including the facility inspection-related deficiencies listed in the Complete Response Letter, dated 16 March 2017, have been satisfactorily resolved by the applicant.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products
ONDP/DNDPI/NDPBI

Attachment A: Life Cycle Knowledge Management
(Next page)
### Lokelma (Sodium Zirconium Cyclosilicate) for Oral Suspension

#### Attribute/CQA

<table>
<thead>
<tr>
<th>Attribute/CQA</th>
<th>Factors that can Impact the CQAs</th>
<th>Initial Risk Ranking</th>
<th>Risk Mitigation Approach</th>
<th>Final Risk Evaluation</th>
<th>Lifecycle Considerations/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay, Stability</td>
<td>Formulation, Container closure, Impurity exceeding specification, Process parameters, Scale/equipment/site</td>
<td>Low (L)</td>
<td>Definitions of the active moiety and the drug substance are acceptable. Assay, and the levels of impurities are controlled by acceptable drug substance/product specifications</td>
<td>Acceptable</td>
<td>These CPPs will need to be examined to evaluate any post market request</td>
</tr>
<tr>
<td>Physical stability (solid state)</td>
<td>Formulation, Raw materials, Process parameters, Scale/equipment/site</td>
<td>Moderate (M)</td>
<td>Product stability has been demonstrated. The control strategy for controlling the levels is adequate</td>
<td>Acceptable</td>
<td>Astra Zeneca Pharmaceuticals LP, Coppell TX site</td>
</tr>
</tbody>
</table>

Reference ID: 4268128
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<th>Attribute/ CQA</th>
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</thead>
</table>
| Content uniformity and potassium exchange capacity (KEC) | • Formulation  
  • Particle size  
  • Segregation  
  • Raw materials  
  • Process parameters  
  • Scale/equipment/site | Moderate (M) | Particle size, a CQA, is controlled by specification. The drug product is water-insoluble and not systemically absorbed. The product’s KEC, a measurement of the in-vitro activity of the product, is acceptable | Acceptable | Changes to formulation, manufacturing process, or product specification will need to be evaluated for impact on the identified product CQAs |
| Microbial limits                         | • Moisture  
  • Process parameters  
  • Scale/equipment/site | Low (L) | Typical microbial testing is performed on product release; the microbial recovery for total aerobic count has been validated per USP<61> and USP<1227>. | Acceptable | Changes to raw materials, formulation, manufacturing site, and process should be evaluated for impact on microbial contamination |
| Palatability                             | • Formulation  
  • Failure to mask unpleasant taste or smell  
  • Excipient change | Moderate (M) | Because of input from the clinical review team, it was determined that based on experience from clinical trials involving adult subjects/patients, there were no palatability concerns regarding this formulation | Acceptable | we may require that the applicant provide in-use stability data (12 - 24 hrs) to demonstrate stability of the product when administered with food (milk, baby food, yogurt etc). Given that the above-specified food items contain potassium, there is potential of potassium from the food items getting entrapped by Lokelma and, thereby, somewhat compromising the potassium binding/trapping ability of Lokelma prior to administration |

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</tr>
</thead>
</table>
| Dosing accuracy | • Formulation  
• Dosing device  
• Process parameters  
• Scale/equipment/site | Moderate (M) | No dosing accuracy-related concerns were identified during the NDA review | Acceptable |