DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021201/S-002

SUPPLEMENT APPROVAL

Merz Pharmaceuticals, LLC
Attention: Misty M. D'Ottavio, RN
Director, Regulatory Affairs
6501 Six Forks Road
Raleigh, NC 27615

Dear Ms. D'Ottavio:

Please refer to your Supplemental New Drug Application (sNDA) dated and received February 2, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Asclera (polidocanol) 0.5% and 1% solution in 2mL glass ampules.

We also refer to our letter dated January 5, 2018, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for polidocanol. This information pertains to the risk of adverse neurologic, cardiac, and embolic events associated with the use of Asclera.

We acknowledge your submission dated February 20, 2018, containing a Dear Healthcare Provider letter to be distributed by March 31, 2018.

This supplemental new drug application provides for revisions to the labeling for Asclera consistent with our January 5, 2018 letter (additions are shown as underlined text and deletions are shown as ~~strikethrough~~ text):

1. In **HIGHLIGHTS** the following text was added:

RECENT MAJOR CHANGES

Warnings and Precautions, Venous Thrombosis and Pulmonary Embolism (5.2)	02/2018
Warnings and Precautions, Arterial Embolism (5.3)	02/2018
Warnings and Precautions, Tissue Ischemia and Necrosis (5.4)	02/2018

WARNINGS AND PRECAUTIONS

- Be prepared to treat anaphylaxis. (5.1)
- Venous Thrombosis and Pulmonary Embolism. (5.2)
- Arterial Embolism.(5.3)
- Tissue ischemia and necrosis: Do not inject intra-arterially. (5.4)
- ~~Do not inject intra-perivascularily. (5.3)~~

2. Under **WARNINGS AND PRECAUTIONS**, the following revisions were made:

5.2 Venous Thrombosis and Pulmonary Embolism
Asclera can cause venous thrombosis and subsequent pulmonary embolism or other thrombotic events. Follow administration instructions closely and monitor for signs of venous thrombosis after treatment. Patients with reduced mobility, history of deep vein thrombosis or pulmonary embolism, or recent (within 3 months) major surgery, prolonged hospitalization or pregnancy are at increased risk for developing thrombosis.

5.3 Arterial Embolism
Stroke, transient ischemic attack, myocardial infarction, and impaired cardiac function have been reported in close temporal relationship with polidocanol administration. These events may be caused by air embolism when using the product foamed with room air (high nitrogen concentration) or thromboembolism. The safety and efficacy of polidocanol foamed with room air has not been established and its use should be avoided.

5.4 Tissue Ischemia and Necrosis
Intra-arterial injection or extravasation of polidocanol can cause severe necrosis, ischemia or gangrene. ~~If this~~ Care should be taken in intravenous needle placement and the smallest effective volume at each injection site should be used. After the injection session is completed, apply compression with a stocking or bandage and have patients walk for 15-20 minutes. If intra-arterial injection of polidocanol occurs, consult a vascular surgeon immediately.

~~**5.3 Inadvertent Perivascular Injection**~~
~~Inadvertent perivascular injection of Asclera can cause pain. If pain is severe, a local anesthetic (without adrenaline) may be injected.~~

3. The Table of Contents, the distribution data, and the revision date were updated.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the

addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Lori Anne Wachter RN, BSN, RAC
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling