

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-201s000

APPROVAL LETTER



NDA 021201

NDA APPROVAL

Chemische Fabrik Kreussler & Co., GmbH.
Attention: Stephan Travers, M.D.
Rheingaustrasse 87-93
D-65203 Wiesbaden
Germany

Dear Dr. Travers:

Please refer to your new drug application (NDA) originally submitted October 1, 1999, withdrawn December 1, 1999, and resubmitted September 29, 2003, and July 10, 2009, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Asclera (polidocanol) 0.5% and 1% Injection.

We acknowledge receipt of your submissions dated July 13, August 19, 20, September 30, November 12, 13 (three), December 3, 10, 15, 16, 28, 30, 2009 and January 7 (two), 12, March 12, 2010.

The July 10, 2009 submission constituted a complete response to our August 2, 2004 action letter.

This new drug application provides for the use of Asclera (polidocanol) to sclerose uncomplicated spider veins (varicose veins ≤ 1 mm in diameter) and uncomplicated reticular veins (varicose veins 1 to 3 mm in diameter) in the lower extremity.

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

STABILITY COMMENTS

Based on the drug substance stability data and in accordance with ICH Q1E, we grant a (b) (4) month retest period for the polidocanol drug substance stored in aluminum canisters with aluminum screw cap closures sealed with a (b) (4) ring.

Based on the drug product stability data and in accordance with ICH Q1E, we grant a 36 month drug product expiry for both 0.5% and 1% Asclera™ (polidocanol) Injection when stored in 2mL, Type I glass, single use, sealed ampoules and stored at USP controlled room temperature (15°C – 30°C (59°F – 86°F)).

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling. For administrative purposes, please designate this submission, **“SPL for approved NDA 021201.”**

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission **“Final Printed Carton and Container Labels for approved NDA 021201”** Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. Varicose veins of the lower extremities is a disease that is not present in the pediatric population.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug applications to conduct postmarketing requirements for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of anaphylaxis or death.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR # 1612-1

1. An assessment of spontaneous reports of anaphylaxis or death associated with Asclera (polidocanol). Following approval, and according to the following timetable, submit a yearly report (containing both interval-based and comprehensive data) analyzing spontaneous adverse event reports received that describes anaphylaxis or death. Cases of anaphylaxis or death should be submitted as 15-day reports.

Interim Report Submissions:	03/2011
	03/2012
	03/2013
	03/2014
	03/2015
Final Report Submission:	03/2016

Submit the letter to your IND 035139, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of the commitments required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any commitment otherwise undertaken to investigate a safety issue. Failure to submit an annual report for the commitments required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

ADVISORY COMMITTEE MEETING

Your application was not referred to an advisory committee because the clinical study design was acceptable, the application did not raise significant safety or efficacy issues, the application

did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of a disease, and outside expertise was not necessary.

PROMOTIONAL MATERIALS

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package inserts, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

LETTERS TO HEALTH CARE PROFESSIONALS

We acknowledge your plan to issue a “Dear Health Care Professional” at the time of product launch identifying:

- a) How Asclera is indicated
- b) How Asclera is not indicated
- c) A description of the risks (e.g., anaphylaxis that might lead to death)
- d) Advice on how to manage the risks (adequate setting, having proper equipment and medication available, etc...) should they occur

We request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-301-1952.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:

Agreed upon labeling

Cc:
INC Research
Attn: Howard Smith, US Agent
675 Peter Jefferson Parkway
Suite 120
Charlottesville, VA 22911

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER & CO. GMBH	Asclera (polidocanol) 0.5%/1%

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

/s/

ROBERT TEMPLE
03/30/2010