CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-201s000

OTHER ACTIONS LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-201

Chemische Fabrik Kreussler & Co., GmbH
c/o INC Research
Attention: Howard M. Smith
Senior Director, Regulatory Operations & Medical Writing
675 Peter Jefferson Parkway
Suite 120
Charlottesville, VA 22911

Dear Mr. Smith:

Please refer to your new drug application (NDA) dated September 29, 2003, received October 2, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aethoxysklerol (polidocanol) Injectable, 0.5%, 1%. (b) (4)

We acknowledge receipt of your submissions dated November 17, and 24, December 5, 9, and 22, 2003; and January 29 (2), February 6, 9, 11, and 25, March 8 and 25, April 7, and May 25, June 1 and 2, 2004.

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Clinical:

1. Efficacy

The efficacy of Aethoxysklerol has not been demonstrated for the proposed indication, sclerotherapy of varicose veins of the lower extremities. The two pivotal trials were designed to evaluate whether Aethoxysklerol was superior to Sotradecol; however, superiority was not demonstrated for the primary efficacy parameter, complete disappearance of varicosities. Furthermore, non-inferiority of Aethoxysklerol to Sotradecol was not established because the treatment effect of the active control (Sotradecol) was not well-characterized in the similar patient population.

2. Safety

An adequate risk-benefit analysis has not been supported by the data provided in this application. The safety data submitted permit little to no assessment for risk of deep vein thrombosis (DVT) following treatment with Aethoxysklerol. None of the studies specifically assessed for DVT post-treatment (e.g., Duplex ultrasound), and DVT has been reported following sclerotherapy, including following treatment of telangiectasias.

The frequent occurrence of superficial vein thrombosis in both treatment groups of all vein sizes might indicate a systemic deficiency in study conduct, e.g., insufficiently detailed study procedures in regard to post-treatment compression.

3. Data Quality and Data Integrity

Upon the Division of Scientific Investigations (DSI) inspection and review, the clinical data and patient records from the sites conducted under the "MICA Study" were determined inadequate and insufficient and thus, cannot be relied upon to support the approvability of this application. From these sites, there is insufficient documentation to assure the data quality or integrity of the following points:

a. All subjects fulfilled the eligibility criteria.
b. The enrolled subjects received the assigned study medication in the dose specified by the protocol.
c. The primary clinical efficacy endpoints were appropriately recorded and verifiable.
d. All enrolled subject were available for the duration of the study and completed the clinical trial.

Chemistry, Manufacturing and Control Microbiology:

The controls are inadequate to prevent microorganisms surviving the sterilization procedures for the product.

Clinical Pharmacology and Biopharmaceutics:

Based on the DSI inspection of the pivotal pharmacokinetic (PK) study, ASK-00-01-00, results from this study (as noted above in the Data Quality and Data Integrity deficiency) cannot be used to meet *in vivo* bioavailability requirements under 21CFR320.

Information needed to resolve non-approvability issues:

Clinical:

1 Efficacy

Conduct two well designed multi-center, randomized, double-blind, vehicle-controlled superiority studies designed to demonstrate safety and efficacy of Aethoxysklerol for treatment of varicosities (stratified by vein size) of the lower extremities. Specifically:

a. Submit durability of treatment effect at one year after the last sclerotherapy session at the time of NDA submission.
b. Include in the protocol a two year follow-up period with reporting either pre- or post-approval. Clearly document and delineate the sclerotherapy technique and safety monitoring for deep vein thrombosis in the protocol.
c. Base blinded efficacy assessment on clinical observation rather than photographs alone.

2. Safety

The clinical studies should also be designed to address the following safety issues:

a. Employ structured and open-ended approaches in the collection of adverse event data, and collect the data at specified time-points post-treatment to permit assessment of the status of the event at a particular time-point.

b. Include safety monitoring collection of laboratory data (hematology, chemistries, urinalysis), electrocardiograms, and post-treatment assessment for deep vein thrombosis (e.g., duplex ultrasound).

c. Collect safety data for a minimum of 300 subjects treated with the highest concentration proposed for marketing be included in the application. Further, evaluate such studies for the specific location of each vein with regard to the major veins treated. Give consideration to the safety and efficacy associated with treating each of these veins. Purely basing approvability on size may discount the potential for larger veins below the knee to respond differently than larger veins above the knee. The known science of venous anatomy of the lower extremities should be used to our maximum advantage in evaluating this product.

d. In addition, submit additional information for safety regarding:

i. cardiac arrhythmias that result from exposure to this drug product

ii. the gradient effect of intravenous injection of this drug

e. Provide additional population definition for which this product should be used or should be contraindicated in (e.g., patients taking disulfuram, patients with certain congenital heart defects, patients who are also being treated with certain anesthetics).

3. Data Quality and Data Integrity

Conduct and monitor all new clinical studies to assure compliance with all federal regulations and statutes, including 21 CFR 312 Part D – Responsibilities of Sponsor and Investigators.

Chemistry, Manufacturing and Control Microbiology:

Provide the following information:

1. The methods used to control and monitor production sterilization cycles in the (b) (4) (b) (4)

2. A statement as to whether or not the product will be reprocessed.

3. An adequate description or diagram of (b) (4) or biological indicator placement within the validation load.

4. A statement as to whether or not the biological indicators were placed directly into the drug product during validation cycles.

5. The D-value of the biological indicators in the drug product or master solution should be provided to prove that the sterilization cycle has been adequately validated.

6. Incubation parameters for the biological indicators after sterilization validation cycles.

In addition, all the facilities listed in this application must be in cGMP compliance.

Clinical Pharmacology and Biopharmaceutics:

Conduct a new *in vivo* bioavailability study with the to-be-marketed formulation of Aethoxysklerol in a sufficient number of patients and in compliance with all federal regulations and statutes, including 21 CFR 312 Part D – Responsibilities of Sponsor and Investigators.

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 non-clinical and clinical studies 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 of Aethoxysklerol.

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 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 study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study 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 a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120.
If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

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 Frank H. Cross, Jr., M.A., MT (ASCP), CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonca Bull, M.D.
Director
Office of Drug Evaluation V
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/

Jonca Bull
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