CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-201s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA Number	21201 # 54, 59 Resubmission
Submission Type; Code	NDA; NME; P
Applicant Name	Kreussler & Co. GmbH, Wiesbaden, Germany
Submission Date	October 1,1999, October 2, 2003, July 21, 2008, July 10, 2009
Brand Name	Asklera™
Generic Name	Polidocanol
Dosage Form	Solution of Aethoxysklerol
Dosage Strengths	0.5% and 1.0% Aethoxysklerol Solutions
Proposed Indication	Sklerotherapy of C1 Veins (b) (4) Very Small Varicose Veins ≤ 1 mm in Diameter) and Reticular Veins (Small Varicose Veins (b) (4) 1 to 3 mm in Diameter) in the Lower Extremity
PDUFA Date	January 10, 2010
OND Division	DCRP
OCP Division	1
Primary Reviewers	Peter H. Hinderling, M.D.
Team Leader	Rajanikanth Madabushi, Ph.D.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY 2

1.1 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS 4
1.2 RECOMMENDATION 4

2. QUESTION BASED REVIEW 4

2.1 GENERAL ATTRIBUTES OF THE DRUG 4
2.2 GENERAL CLINICAL PHARMACOLOGY 6

2.3. INTRINSIC FACTORS.....11
2.4. EXTRINSIC FACTORS.....12
2.5 ANALYTICAL SECTION 14
3. LABEL RECOMMENDATIONS.....15
4. INDIVIDUAL STUDY REPORT 35

1. EXECUTIVE SUMMARY

The sponsor Kreussler & Co.GmbH, Wiesbaden, Germany, seeks market approval for 0.5% and 1.0% solutions of aethoxysklerol for the treatment of spider and reticular varicose veins. The drug product is given by intravenous injection into affected veins. The drug substance polidocanol, a polyethylene glycol monododecylether, by sclerosing the venous intima, obliterates affected veins thereby improving the aesthetic appearance. From 0.1 to 0.3 mL of the respective solutions per vein are to be injected into affected spider and reticular veins. These volumes correspond to polidocanol doses of 0.5-1.5 mg for spider veins and 1.0-3.0 mg for reticular veins. The proposed label states (b) (4)

Regulatory History

The original submission of this NDA was in 1999. Shortly thereafter it was withdrawn due to no-validated pharmacokinetic data. Resubmissions were submitted in 2003 and 2008. In the 2003 submission results of a new bioavailability study were included, but found to be inacceptable. The 2008 submission was deemed not to be filable, because the sterilization validation information was not acceptable in the current state of transition from (b) (4) In addition, there were issues with the sterility information. A more detailed regulatory history can be found on p.4 of Section 2.1 of the QBR.

2009 Resubmission

The 2009 resubmission contained the results of a placebo controlled, randomized clinical trial using solutions of 0.5% aethoxysklerol, 1.0% aethoxysklerol, sodium tetradecyl sulfate (sotradecol®) 1% and placebo (isotonic NaCL solution) for the treatment of C1 venous insufficiency spider and reticular veins (EASI trial). This was a multi-center study. The primary objective of the study was to demonstrate efficacy of polidocanol in the treatment of C1 veins compared to placebo. The secondary objective of the trial was

to demonstrate efficacy of polidocanol compared to sodium tetradecyl sulfate and the tertiary objective was to determine the pharmacokinetics of polidocanol in subjects receiving the aethoxysklerol treatment. The primary endpoint was the improvement of the treated veins in accordance with a 5 grade scale evaluated relative to placebo by a blinded investigator and two independent also blinded medical experts 12 weeks after the last injection of aethoxysklerol.

PK Sub-study of the EASI Trial

The pharmacokinetic study enrolled 22 patients, 12 with spider veins and 10 with reticular veins. The respective volumes of aethoxysklerol 0.5% and 1.0% injected ranged between 0.33 and 1.9 mL and 1.3 and 2.0 mL, respectively. These volumes correspond to respective doses of polidocanol ranging between 1.5 and 9.0 mg injected into spider veins and ranging between 13 and 20 mg of polidocanol injected into reticular veins. The dose range of polidocanol used in the pharmacokinetic sub-study of 1.5-20.0 mg was in agreement with the dose range for aethoxysklerol 0.5% and 1.0% used in the clinical trial (respective median doses of 4.5 mg and 15 mg injected into spider veins and reticular veins, respectively). The sponsor proposed maximum dose for a single injection is (b) (4) (b) (4) for a treatment day/session.

The first blood sample was collected 5 min after injection. Additional samples were collected up to 6 h after injection. The plasma concentrations of polidocanol were measured by a validated LC-MS/MS assay. The PK parameters determine by the sponsor showed unusual inter-subject variability. The dose normalized AUC and Cmax values after the lower dose in patients with spider veins exceeded those after the higher dose of aethoxysklerol in patients with reticular veins. Sixteen (16) patients (10 with spider veins, 8 with reticular veins) displayed pre-dose plasma concentrations that exceeded 10 ng/mL, the LLOQ of the assay, significantly. The positive pre-dose levels were 2 to 67% of Cmax. In 8 patients with spider veins the extrapolated AUC was more than 20% of AUC. Because of the positive pre-dose plasma concentrations and the large contribution of the extrapolated AUC to total AUC the estimates for AUC must be considered biased. The sponsor could not provide an explanation for the positive pre-dose plasma concentrations. In addition, there was evidence indicating that the blood sampling schedule was not adequate for accurately determining true Cmax.

Based on these findings acceptability criteria for the data were set up by the Reviewer. Only data from subjects with negative pre-dose concentrations and extrapolated areas < 0.2 ● AUC were considered reliable. The data in only 4 of the 22 subjects met the Reviewer's acceptability criteria. Of the parameters determined in the 4 subjects only t1/2 can be considered reliable and should be reported. As stated above, the sampling schedule was inadequate for determining true Cmax. Because of local entrapment aided by compression the amounts of polidocanol reaching the systemic circulation may be significantly smaller than the dose administered limiting the interpretability of CL and Vss.

In conclusion, the bioavailability study conducted by the sponsor shows two major deficiencies: The dose levels tested are considerably lower than the maximum dose of (b) (4) proposed by the sponsor for polidocanol for a treatment day/session and the reliable PK information obtained at the lower dose levels is very limited.

1.1 Summary of Important Clinical Pharmacology Findings

The doses of polidocanol used in the pharmacokinetic sub-study of EASI are ≤ 20 mg whereas the maximum dose proposed by the sponsor for a treatment session/day is (b) (4) mg. Therefore, the sponsor has not established exposure and bioavailability of polidocanol at dose levels used under the typical conditions of a treatment day/session.

The PK parameter estimates for polidocanol in18 of the 22 patients studied cannot be considered reliable. The PK information obtained in the 4 subjects whose data met the acceptability criteria is limited to a reliable estimate of mean t1/2. Blood samples were not frequently enough collected to determine true Cmax. Because of local entrapment the amounts administered and systemically available may differ significantly limiting the interpretability of clearance and volume of distribution.

1.2 Recommendation

The results of the bioavailability study performed by the sponsor are not acceptable regarding PK parameters of primary interest, i.e. Cmax and AUC. The elimination half-life could be estimated from 4 subjects with evaluable data and should be reported in the label. Given that the safety data base of polidocanol in humans is unremarkable, the value of the information gained by a repeat bioavailability study is uncertain. Thus, a new bioavailability study is not warranted.

2. QUESTION BASED REVIEW

2.1 General attributes of the drug

What is background?

Polidocanol is the drug substance in aethoxysklerol®, the drug product.

What is regulatory background or history?

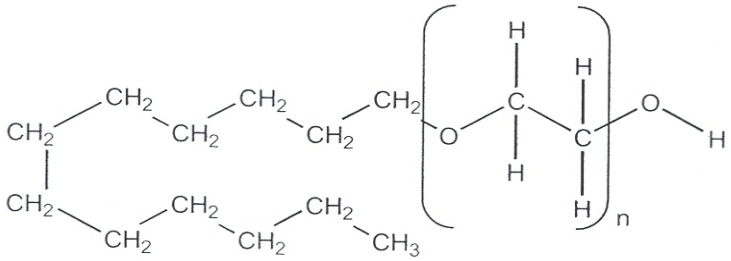
Aethoxysklerol® is marketed in several European countries. Sklerosing agents other than Aethoxysklerol® are marketed in the US.

The original submission of this NDA was in 1999. Shortly thereafter it was withdrawn due to no-validated pharmacokinetic data. Resubmissions were submitted in 2003 and 2008. In the 2003 submission results of a new bioavailability study were included. The deficiencies noted were in the Medical and Clinical Pharmacology sections. In the pivotal trial neither superiority, nor non-inferiority of aethoxysklerol relative to the active comparator, sodium tetradecyl sulfate, could be demonstrated, and a non-approvable recommendation was made by the Division of Dermatology and Dental Drug Products. The bioavailability study was performed in Japan and the report of the Division of Scientific Investigation determined the following deficiencies at the analytical site: failure to quantitate the analyte following each wash during analysis of subject plasma analysis, failure to select adequate QC levels and failure to collect data in a secure manner. At the clinical site the deficiencies included failure to maintain proper documentation of source documents, missing several blood draws in 2 subjects, and failure to establish criteria for the actually administered dose in subjects, within the dosing range specified by the protocol. The Clinical Pharmacology Review concluded that the sponsor needs to repeat the bioavailability study with the marketed formulation because of deficiencies at the clinical and analytical site.
The 2008 submission was deemed not to be filable, because the sterilization validation information was not acceptable in the current state of transition from (b) (4) (b) (4) (b) (4) In addition there were issues with the sterility information.

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Drug Substance

The drug substance is polidocanol (lauromacrogol 400), a polyethylene glycol consisting of twio components: a polar, hydrophilic (dodecyl alcohol) and an apolar hydrophobic (polyethylene oxide) chain. It is an aggregate with different degrees of polymerization. The MW of polidecanol is approximately 600 and the structure is a follows:



$C_{12}H_{25}(OCH_2CH_2)_nOH$ Polyethylene glycol monododecyl ether
Mean extent of polymerization (n) : Approximately 9
Mean molecular weight : Approximately 600

The mean extent of polymerization is approximately n=9.

Drug Product

The drug product is an injection solution of 2 strengths of aethoxysklerol: 0.5% solution containing 5 mg/mL or 1% solution containing 10 mg/mL water with 5% (v/v) ethanol at pH 6.5-8.0;disodium hydrogen phosphate dehydrate and potassium dihydrogen phosphate are added for pH adjustment as shown in the below table:

Table 1. Clinical Formulation (per 2 mL drug product).

Component	Aethoxysklerol 0.5%	Aethoxysklerol 1.0%
polidocanol	10.00 mg	20.00 mg
96% EtOH	84.00 mg	84.00 mg
(b) (4) sodium phosphate	2.40 mg	4.80 mg
(b) (4) potassium phosphate	0.86 mg	1.70 mg
water for injection		
(b) (4)		

Aethoxysklerol 0.5%, 2 mL of 0.5% solution for injection contain 10 mg polidocanol, maximum dose per treatment session is (b) (4) aethoxysklerol 0.5%
Aethoxysklerol 1.0%, 2 mL of 1% solution for injection contain 20 mg polidocanol, maximum dose per treatment session is (b) (4) aethoxysklerol 1.0%.

Aethoxysklerol is manufactured by (b) (4)

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Polidocanol is a detergent sclerosing agent that locally damages the endothelium of blood vessels. When injected intravenously it destroys the injected varicose vein through sequential actions: First, the drug induces endothelial damage. Then, platelets aggregate at the site of damage and attach to the venous wall. Eventually, a dense network of platelets, cellular debris, and fibrin occludes the vessel, and finally the obliterated vein is replaced with connective tissue.

The therapeutic indication for aethoxysklerol is sclerotherapy of spider veins (b) (4) very small varicose veins, ≤ 1 mm in diameter) and reticular veins (small varicose veins (b) (4) 1-3 mm diameter) in the lower extremity.

2.2 General clinical pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor performed a prospective randomized, placebo and active comparator controlled, double-blind, comparative, multi-center study. PK assessment in a subgroup was performed open-label in one center. The pivotal efficacy and safety study included 4 treatment arms 1) Aethoxysklerol 0.5% 2) Aethoxysklerol 1% 3) Sotradecol® and 4) placebo (isotonic saline) in 108 patients presenting with spider veins and 108 patients with reticular veins. Injections of Aethoxysklerol 0.5% (reticular veins) or 1% (spider veins) could be given to the veins of a predetermined area of one leg. A repeat injection could be given three and six weeks later if the previous injection was evaluated as unsuccessful by the investigator. The primary endpoint was improvement of veins judged by the blinded investigator and two blinded independent medical experts. Digital images of the treatment areas were taken at screening, prior to the injection, compared with those taken 12 weeks post-treatment and rated on a 5 point scale.

2.2.2 What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics PD) and how are they measured in clinical pharmacology and clinical studies?

Clinical endpoints were used. The primary endpoint was improvement of veins judged by the blinded investigator and two blinded independent medical experts based on digital images of the treatment areas taken prior to the injection and 12 weeks after the last injection. The pictures were rated based on a 5 point scale as follows:

- 1 is "worse than before" (more veins in the treatment area are observable than before or veins are more dilated or looked worse than before)
- 2 is "same as before" (no improvement but also no worsening observable)
- 3 is "moderate improvement" (improvement observable but not yet satisfactory, needs to be treated again)
- 4 is "good improvement" (satisfactory treatment success, only slight improvement still possible)
- 5 is "complete treatment success" (no improvement necessary)

The median of these values was representative for each individual patient.

Secondary efficacy variables were:

1) Patient satisfaction with the treatment after **12** (± 2) weeks. Comparison between Aethoxysklerol® and placebo.
2) Assessment of the treatment success **12** (± 2) weeks after the last injection. Comparison between Aethoxysklerol® and placebo.
3) The assessment of improvement of veins according to a 5-grade scale made **26** weeks (± 4 weeks) after last injection; the same statistical test was performed as for the primary efficacy parameter. Comparison between Aethoxysklerol® and placebo (isotonic saline).
4) Patient satisfaction with the treatment after **26** (± 4) weeks. Comparison between Aethoxysklerol® and placebo.
5) Assessment of the treatment success **26** (± 4) weeks after the last injection. Comparison between Aethoxysklerol® and placebo.
6) The assessment of improvement of veins according to a 5-grade scale made **12** weeks (± 2 weeks) after last injection. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.
7) Patient satisfaction with the treatment after **12** ± 2) weeks. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.
8) Assessment of the treatment success **12** (± 2) weeks after the last injection. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.
9) The assessment of improvement of veins according to a 5-grade scale made **26** weeks (± 4 weeks) after last injection. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.
10) Patient satisfaction with the treatment after **26** (± 4) weeks. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.
11) Assessment of the treatment success **26** (± 4) weeks after the last injection. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate

The success rate was derived from the 5 grade-scale where treatment success was grade 4 and 5 and treatment failure grade 1-3 on the following 5 point rating scale: "5= complete success", 4 = "good improvement", 3="moderate improvement", 2="same as before" and 1="worse than before".

2.2.3 Are the active moieties in plasma (or other biological fluids) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Polidocanol is a polymer. The LC/MS/MS assay measured polidocanol with n=9 monolaurylethers m/z=600.4 and 133.1 were used as Q1 and Q3 massdetection, respectively. The relative activity of the different polidocanol polymers is not known.

The pre-dose plasma concentrations were positive for polidocanol in 16 of the 22 patients. Not enough blood samples were collected immediately after injection of polidocanol for a proper determination of Cmax.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *efficacy*?

No exposure -efficacy analysis was performed.

What is time of onset and offset of the desirable pharmacological response or clinical endpoint?

The onset and offset of the local sclerosing effect of polidocanol is rapid. The effect is irreversible.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety?*

No exposure-safety analysis was performed.

2.2.4.3 Does the drug prolong the QT/QTc interval?

No thorough QT/QTc study was performed. However, the drug is not administered chronically. Therefore, concerns for pro-arrhythmic effects of polidocanol are minor.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose and response, and are there any unresolved dosing or administration issues?

Consistency of dose-response relationship

The injected volume of aethoxysklerol is not significantly diluted by the small blood volume in spider veins and injected and actual concentrations are nearly identical. This contrasts with the condition in reticular veins. The dilution of the injected volumes of aethoxysklerol in larger reticular veins of 2 and 3 mm diameter can be significant so that the actual concentrations are significantly smaller than those in spider veins pointing to the possibility of sub-therapeutic concentrations of aethoxysklerol reticular veins and explain in part why repeat injections are necessary in the EASI trial.

2.2.5 What are the PK characteristics of the drug and its major metabolite(s)

In the 4 evaluable patients apparent peak plasma concentrations of polidocanol are observed 5 minutes after intravenous injection, the time of the first blood sample collection. Thereafter, the plasma concentrations decline with a mean apparent terminal t1/2 of 1.5 h.

2.2.5.1 What are the single and multiple dose PK parameters?

See 2.2.5 for single dose. Polidocanol is not administered in multiple doses.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The PK of polidocanol was not determined in healthy subjects. The patients were in the age range of 40-50 years. The metabolism of polidocanol was not investigated.

2.2.5.3 What are the characteristics of drug absorption (possible transporters and pH impact)

NA

2.2.5.4 What are the characteristics of drug distribution (incl. plasma protein binding)

A reliable estimate is not available.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Mass balance including main elimination routes and possibly circulating metabolites of polidocanol are not known.

2.2.5.6 What are the characteristics of drug metabolism? (extraction ratio, metabolic scheme, enzymes responsible, factional clearances)

The metabolism of polidocanol has not been investigated.

2.2.5.7 What are the characteristics of drug excretion?

The excretion of unchanged polidocanol in urine or bile has not been determined.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Based on the limitations of the available data the degree of linearity/nonlinearity of polidocanol cannot be determined.

2.2.5.9 How do the PK parameters change with time following chronic dosing? (circadian rhythm, self induction, time to steady-state, single dose prediction of multiple dose PK, accumulation ratio)

NA

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Due to limitations of the available data inter-subject or intra-subject variability in the exposure measures Cmax and AUC cannot be reliably assessed.

2.3. Intrinsic factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The impact of the intrinsic factors has not been assessed.

2.3.2 Based on what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

There is no information available on the impact of intrinsic factors allowing rationally based dose adjustments in subpopulations.

2.3.2.1 Elderly

See 2.3.1 and 2.3.2

2.3.2.2 Pediatric patients. Also what is status of pediatric studies and/or any pediatric plan for study?

See 2.3.1 and 2.3.2. Studies in pediatric patients were not conducted and are not planned to be conducted in the future.

2.3.2.3 Gender

See 2.3.1 and 2.3.2

2.3.2.4 Race

See 2.3.1 and 2.3.2

Renal Impairment

See 2.3.1 and 2.3.2

2.3.2.5 Hepatic Impairment

See 2.3.1 and 2.3.2

2.3.2.6 What pharmacogenetic information is there in the application and is it important or not?

There is no pharmacogenetic in formation in the submission.

2.3.2.7 What pregnancy and lactation use information is there in the application?

There is no information on pregnancy or lactation in the submission

2.3.2.8 What other human factors are important to understanding the drug's efficacy and safety?

There are no known other intrinsic factors

2.4. Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or- response and what is the impact of any differences in exposure on response?

The impact of extrinsic factors has not been investigated

2.4.2 Based on what is known about the exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

None

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

No in vitro enzyme or transporter studies have been performed with polidocanol.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

There is no information on metabolites and CYPs or Phase II enzymes involved in the metabolism of polidocanol.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

The induction or inhibition potential of polidocanol has not been determined

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Polidocanol as a potential substrate or inhibitor of P-gp has not been investigated

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

The potential of polidocanol as substrate of enzymes or transporters has not been determined.

2.4.2.6 Does the label specify co-administration of another drug (e.g. combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

No.

2.4.2.7 What other co-medications are likely to be administered to the target population?

The target population undergoing treatment with sclerosing agents is likely to be healthy.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic dug-drug interactions, if any?

No

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

The metabolism of polidocanol has not been investigated. Whether polidocanol generates active metabolites is unknown.

2.4.3 What issues related to dose, dose regimens, or administration are unresolved and represent significant omissions?

The impact of exerting compression on the injection site during and after injection has not been explored. It would be important to know whether the fraction of the dose

escaping into the systemic circulation is substantially reduced by local compression. An experiment could have been done in animals to study the impact of local compression and drug entrapment by injecting polidocanol into a large vein without compression and in a small superficial vein with compression. A difference in AUC would indicate that local compression and/or entrapment have an impact on the amounts of polidocanol systemically available. The result of such a study enables extrapolation of the animal data to human safety

See also 2.2.4.4

2.5 Analytical Section

2.5.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Polidocanol is a polymer containing a mixture of monolauryl ethers with an average n= 9. The LC/MS/MS method measures the polymer with n=9 monolaurylethers. It is unknown whether the different polymers differ in their pharmacological activity.

2.5.2 Which metabolites have been selected for analysis and why?

None

2.5.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total (free + unbound) concentrations are being measured. It is not known whether the plasma protein binding of polidocanol is concentration independent. Therefore, there is no rational basis for measuring total concentrations of polidocanol.

2.5.4 What bioanalytical methods are used to assess concentrations?

LC/MS/MS.(see also 2.2.3

What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The standard curve is linear from 10 ng/mL to 1000 ng/mL. The assay is validated for plasma samples that are diluted tenfold. Weighted least square regressions were used to fit the standard curve.

2.5.4.1 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

10 and 1000 ng/mL, respectively.

2.5.4.2 What are the accuracy, precision, and selectivity at these limits?

The inter-run precision of the LC/MS/MS method determined from the QC samples is ≤ 6.9% and the accuracy ranges between 1.1-2.0% .

2.5.4.3 What is the sample stability under the conditions used in the study (long term, freeze-thaw, sample handling, sample transport, autosampler)?

The stability of apparent polidocanol has been demonstrated under the conditions used in the study.

2.6.4.4 What is the QC sample plan?

QC samples (20, 100 and 800 ng/mL) were analyzed along with the samples of unknown concentrations.

3. LABEL RECOMMENDATIONS

(b) (4)

19 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

17.1 FDA-approved Patient Labeling

PLACE HOLDER

Distributed by:

BioForm Medical, Inc.
4133 Courtney Road, Suite #10
Franksville, WI 53126

Licensed from:

Chemische Fabrik Kreussler & Co. GmbH
65203 Wiesbaden
GERMANY

TRADENAME™ and Aethoxysklerol® are trademarks of Chemische Fabrik Kreussler & Co. GmbH, 65203 Wiesbaden, GERMANY.

4. INDIVIDUAL STUDY REPORT

4.1 Study Report EASI (HCR:1085/KRS) Efficacy and Safety of Aethoxysklerol® Compared to Sodium Tetradecyl Sulfate and Isotonic Saline (Placebo) for the Treatment of Reticular Veins and Spider Veins Including Subgroup to Investigate the Plasma Concentrations of Polidocanol

Investigator and Study Site

Principal Investigator: Prof. Dr. med. Eberhard Rabe, Universitaetshautklinik, Bonn Sigmund-Freud-Str. 25, 53105 Bonn, Germany, and 19 other study sites in Germany

Objectives

Primary

Efficacy of aethoxysklerol in the treatment of C1 veins compared to placebo

Secondary

- Efficacy of aethoxysklerol compared to sodium tetradecyl sulfate
- Safety of aethoxysklerol
- Patient satisfaction with the treatment

Additional Objective

- Assessment of plasma concentrations of polidocanol

Investigational Drugs and Formulations

- Aethoxysklerol 0.5%, 2 mL of 0.5% solution for injection contain 10 mg polidocanol, maximum dose per treatment session is 4.8 mL aethoxysklerol 0.5%, Lot No. 17278; Aethoxysklerol 1.0%, 2 mL of 1% solution for injection contain 20 mg polidocanol, maximum dose per treatment session is 2.4 mL aethoxysklerol 1.0%, Lot No. 17378, manufacturer: (b) (4) (b) (4)

- Sodium tetradecyl sulfate 1% (Sotradecol®), 2 mL of 1.0% solution for injection contain 20 mg sodium tetradecyl sulfate; The maximum dose per treatment session is 2.4 mL (reticular veins) or 4.8 mL (spider veins) sodium tetradecyl sulfate 1.0%, Lot No. 050803, manufacturer: Bioniche Pharma Group Ltd. Sotradecol was bought in the open market in the US and imported into Germany. To maintain blinding, the maximum dose allowed for sodium tetradecyl sulfate 1% was 2.4 mL for subjects with spider veins and 4.8 mL in the subjects with reticular veins for a maximum of 8 and 16 injections per treatment sessions.

- 0.9% isotonic saline solution

Study Design

This is a prospective randomized, placebo and active comparator controlled, double-blind, comparative, multi-center study. PK assessment in a subgroup was performed open-label in one center.

It was planned to evaluate at least 216 patients with C1 veins after treatment with investigational compounds: 108 patients with C1 veins were treated with either aethoxysklerol 0.5% or sodium tetradecyl sulfate 1% or isotonic saline solution and 108 patients with C1 reticular veins were treated with aethoxysklerol 1% or 1% sodium decadecyl sulfate or isotonic saline solution as determined by randomization. The veins in a predetermined area of one leg per patient were treated at Visit 1 by injecting either aethoxysklerol 1% (reticular veins) or aethoxysklerol 0.5 % (spider veins) or sodium tetradecyl sulfate 1% or isotonic saline solution.

The doses of polidocanol were those approved in Germany (b) (4) (b) (4) The maximum dose of aethoxysklerol 1% allowed per treatment session was 2.4 mL in patients with reticular veins and 4.8 mL 0.5 % in the patients with spider veins. These doses were smaller than those proposed by the sponsor as maximum doses for a treatment session/day. To maintain blinding the maximum dose for sodium tetradecyl sulfate 1% was also 2.4 mL in patients with reticular veins and 4.8 mL in patients with spider veins, respectively, for the maximum of 8 or 16 injections per treatment session. Aethoxysklerol and sodium tetradecyl sulfate are clear solutions of similar viscosity as saline solution. Due to their tension active properties they tend to froth when shaken. In order to maintain blinding of the study a non-blinded dedicated member of study personnel who was not otherwise involved in study assessments, prepared the syringe for injection and handed it over to the blinded investigator.
The study medications were injected intravenously. During and after the injections compression was exerted.

The scheduled study activities are listed in the below scheme:

Table 1: Study flow chart

	Visit 0 (Screening)	Visit 1 [1] (1-14 days after screening)	Visit 1a 1 week (± 3 days) after Visit 1	Visit 2 3 weeks (± 7 days) after Visit 1	Visit 2a 1 week (± 3 days) after Visit 2	Visit 3 3 week (± 7 days) after Visit 2	Visit 3a 1 week (± 3 days) after Visit 3	Visit 4 12 weeks (± 2 weeks) after last injection	Visit 5 26 weeks (± 4 weeks) after last injection
					Only performed if 2nd injection is given	Only performed if 2nd injection is given	Only performed if 3rd injection is given		
Informed consent	x								
Documentation of area to be treated	x								
Inclusion and exclusion criteria	x	x							
Personal data and medical history	x								
Physical examination	x								
Vital signs	x	x[2]	x	x[2]	x	x[2]	x	x	x
Pregnancy test if applicable	x	x		x[3]		x[3]			
Clinical laboratory tests	x	x[4]						x	
ECG	x	x[4]							
Ultrasound to exclude DVT	x		x					x	
Thrombophilia testing	x								
Digital image of area to be treated	x	x (before injection)						x	x
Treatment (injection of study medication)		x		x[5]		x[5]			
Micro-thrombectomy			x[6]	x[6]	x[6]	x[6]	x[6]		
Compression stocking [7]		x		x[5]		x[5]			
Blood sampling for concentrations of polidocanol [8]		x						x[11]	
Assessment of change in health and general adverse events		x	x	x	x	x	x	x	x
Evaluation of treatment success by investigator [9]				x		x		x	x

	Visit 0 (Screening)	Visit 1 [1] (1-14 days after screening)	Visit 1a 1 week (± 3 days) after Visit 1	Visit 2 3 weeks (± 7 days) after Visit 1	Visit 2a 1 week (± 3 days) after Visit 2	Visit 3 3 week (± 7 days) after Visit 2	Visit 3a 1 week (± 3 days) after Visit 3	Visit 4 12 weeks (± 2 weeks) after last injection	Visit 5 26 weeks (± 4 weeks) after last injection
					Only performed if 2nd injection is given	Only performed if 2nd injection is given	Only performed if 3rd injection is given		
Assessment of treatment area by investigator and patient		x	x	x	x	x	x	x	x
Current medication	x	x	x	x	x	x	x	x	x
Patient satisfaction [10]								x	x
Patient estimation of drug (placebo or active)								x	x
Appointment for next visit	x	x	x	x	x	x	x	x	
Study closure									x

[1] before visit 1 the results of the laboratory tests and thrombophilia testing must be available
[2] Before and 30 (± 15) min after treatment
[3] only necessary if second or third injection was given
[4] 30 minutes (± 15) after treatment
[5] If according to the investigator there was not complete improvement after the first or second treatment session, (i.e. grade 5 was not achieved) and therefore a second or third treatment was necessary
[6] If deemed necessary
[7] Compression stocking had to be worn for 2 weeks during the day from immediately after the injection but not on the day before the next visit or the day of the visit
[8] Only for group C: before first injection and 5 min, 30 min, 1h, 1.5h, 2h, 3h and 6h after first injection for plasma concentrations of polidocanol.
[9] before treatment in order to evaluate if further treatment was necessary
[10] Patients received the baseline picture (digital image) in order to assess their satisfaction with the treatment
[11] At least one week after the last varicose vein injection, Group C only:
- PK sample
- Questioning about which medications, cosmetics creams, oils, shampoos etc. used during the 7 days prior to the baseline PK sampling and in the 7 days before the additional PK sampling

Thirty minutes after injection an ECG was recorded. Sixty minutes after injection a blood sample was taken for safety clinical laboratory parameters. A repeat injection could be given three and six weeks later if the previous injection was evaluated as unsuccessful by the investigator. Digital photographs were taken at screening (Visit 0), immediately before injection (Visit 1), at 12 ± 2 weeks (Visit 4) and 26 ± 4 weeks (Visit 5) after the last injection. The first follow-up visit was 3 ± 1 weeks after the injection at which time the patients could receive a second injection of the same allocated treatment if the first treatment was not successful, i.e. if the patient was not graded 5 on the 5-grade evaluation scale. The patients could receive a third injection of the same allocated treatment at Visit 3 if the second treatment was not fully successful, i.e. if the patient was not graded 5 on the 5-grade scale. All patients returned to the site for Visit 4 at 12 ± 4 weeks after the last injection, at which time the primary endpoint was assessed and digital images were taken. Also patient satisfaction was evaluated at this time. A final follow-up visit (Visit 5) was at 26 ± 4 weeks after the last injection at which time again digital images were taken and patient's satisfaction evaluated. In order to detect an ongoing deep vein thrombosis (DVT), patients were checked for DVT at Visits 1a and 4. Microthrombectomy was performed if necessary at Visit 1a, 2, 2a, 3 and 3a.

The primary endpoint was the improvement of the treated veins in accordance with a 5 grade scale 12 ± 2 weeks after the last injection comparison between aethoxysklerol and placebo). The 5 grade scale used was as follows:

- 1 is "worse than before" (more veins in the treatment area are observable than before or veins are more dilated or looked worse than before)
- 2 is "same as before" (no improvement but also no worsening observable)
- 3 is "moderate improvement" (improvement observable but not yet satisfactory, needs to be treated again)
- 4 is "good improvement" (satisfactory treatment success, only slight improvement still possible)
- 5 is "complete treatment success" (no improvement necessary)

Secondary efficacy variables included the following:

Secondary efficacy variables were:

1) Patient satisfaction with the treatment after **12** (± 2) weeks. Comparison between Aethoxysklerol® and placebo.
2) Assessment of the treatment success **12** (± 2) weeks after the last injection. Comparison between Aethoxysklerol® and placebo.
3) The assessment of improvement of veins according to a 5-grade scale made **26** weeks (± 4 weeks) after last injection; the same statistical test was performed as for the primary efficacy parameter. Comparison between Aethoxysklerol® and placebo (isotonic saline).
4) Patient satisfaction with the treatment after **26** (± 4) weeks. Comparison between Aethoxysklerol® and placebo.
5) Assessment of the treatment success **26** (± 4) weeks after the last injection. Comparison between Aethoxysklerol® and placebo.
6) The assessment of improvement of veins according to a 5-grade scale made **12** weeks (± 2 weeks) after last injection. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.
7) Patient satisfaction with the treatment after **12** (± 2) weeks. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.
8) Assessment of the treatment success **12** (± 2) weeks after the last injection. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.
9) The assessment of improvement of veins according to a 5-grade scale made **26** weeks (± 4 weeks) after last injection. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.
10) Patient satisfaction with the treatment after **26** (± 4) weeks. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.
11) Assessment of the treatment success **26** (± 4) weeks after the last injection. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate

The **success rate** was derived from the 5-grade-scale where treatment success was grade 4 or 5 on the 5-point scale and treatment failure was grade 1, 2 or 3 on the 5-point scale.

Patient satisfaction was assessed as described below:

The patients rated their satisfaction with the current treatment at Visit 4 and 5 using the following verbal rating scale; the assessment was to be made by allocation to one of the five categories:

(1) very unsatisfied
(2) somewhat unsatisfied
(3) slightly satisfied
(4) satisfied
(5) very satisfied

At the time of their evaluation, the patients received the digital images of the treatment area taken at Visit 1.

The safety variables included the assessment of the treatment area, pain and subjective sensations as follows:

Pain during treatment session at Visit 1 (and 2 and 3 if applicable)

The patient was asked whether he/she has experienced pain:
(1) during injection (irrespective of its degree)
(2) 2 minutes after the injection

The pain 2 minutes after injection was rated according to the following 5 grade scale:
(1) Extremely severe
(2) Severe
(3) Moderate
(4) Mild
(5) None

Investigator's assessments at Visits 1,1a 2, (2a, 3 and 3a if applicable), 4 and 5

At each visit the investigator assessed the treated area for the presence of each of the following signs:

- Hyperpigmentation
- Hematoma
- Neovascularization
- Other

The symptoms were marked as present or absent.

Subjective sensations at Visits 1, 1a 2, (2a and 3, 3a if applicable), 4 and 5

The patient was asked whether he/she has experienced the following sensations in the area of treatment immediately after and approximately 0.5 hours after the injections at Visit 1 (and if applicable Visit 2 and Visit 3) and since the last assessment at Visit 1a, 2a, 3a, 4 and 5:

- Itching
- Pain
- Warmth
- Burning
- Other

The sensations were rated on the following 5-point scale:
(1) Extremely severe
(2) Severe
(3) Moderate
(4) Mild
(5) *None*

Pharmacokinetic Profiling

The pharmacokinetic sub-study was performed under open-label conditions and the patients received only aethoxysklerol 0.5% or 1%. Blood samples were taken for the determination of the plasma concentrations of polidocanol from 10 patients presenting with reticular veins and 12 patients with spider veins at one specific center (Group C) at Visit 1. Blood samples were collected from an antecubital vein pre-dose (10-20 min before infusion) and 5, 30, 60, 90, 120, 180 and 360 min after start of the injections. The report does not indicate which vein was punctured for collecting the blood samples. A non-scheduled additional blood sample was collected at Visit 4 at least one week after the last varicose vein injection visit. The patients were asked in detail about which medications, cosmetics creams, oils, shampoos etc. they used during the 7 days prior to the baseline sampling for polidocanol and during the 7 days before the additional blood sampling on Visit 4. The query did not provide evidence that could explain the positive pre-dose samples.

Bioassay

The plasma concentrations of polidocanol were measured by ACC GmbH Analytical Clinical Concepts, D-63849 Leidersbach, Germany. A validated LC/MS/MS method after solid phase extraction was used. The important characteristics of the method are summarized in the below table:

11.1.5 CHROMATOGRAPHIC CONDITIONS

(b) (4) was used as internal standard. The standard curve was linear (weighted least square linear regression) within the range of 10 ng/mL and 1000 ng/mL. The coefficient of correlation was ≥ 0.9934. The LLOQ of the standard curve was 10 ng/mL and the ULOQ is 1000 ng/mL. The high, medium and low QC samples were 800 ng/mL, 100 ng/mL and 20 ng/mL, respectively. A run was accepted, if at least six of the nine QC samples were within ± 15% from the nominal value. Inter-run mean precision of the method with the QC samples run along the plasma samples of unknown concentrations was ≥ 6.9% and inter-run mean accuracy ranged between 1.1 and 2.0%. Samples with concentrations in excess of 1000 ng/mL were diluted with blank plasma 1:10. Plasma samples spiked to get a concentration of 4000 ng/mL polidocanol and then diluted 1:10 with blank plasma exhibited a mean precision of 1.9% and accuracy of 3.2%.

Stability of polidocanol and the internal standard in the stock solution for 6 h at room temperature and up to 20 days at 2-8 º C was demonstrated. The stability of polidocanol for 6 months at -20 º C, 6 h at room temperature and through 3 freeze/thaw cycles was also demonstrated using QC samples spiked with 800 ng/ml and 20 ng/mL polidocanol. Finally, stability of polidocanol and the internal standard in the final extract left for 24 h in the auto-sampler was shown using spiked QC samples.

The analysis of plasma samples spiked with polidocanol showed no interference from endogenous compounds. Polidocanol is a polymer, a mixture of monolauryl ethers of macrogols with an average n=9. The LC-MS/MS method was developed to determine polidocanol with n=9.

Eleven (11) % of the samples (pre-dose samples) were re-assayed twice, because of the measured positive values in some of the subjects, the sponsor suspected a possible mix-up of the samples. Reporting of the final concentration value for these samples was performed in accordance with the analytical laboratory's SOPs. Three (3) % of the samples measured 5 or 6 minutes after injection were re-assayed because the concentrations exceeded the ULOQ.

PK Data Analysis

A non-compartmental data analysis was performed using WINNONLIN. The following parameters were computed: Cmax, tmax, tlast, λz, t1/2, AUC0-tlast, AUC0-inf (=AUC(0-tlast) + Clast/λz . At least 3 concentration data points in the apparent terminal log linear phase were used to determine λz from the slope. AUC0-tlast was determined using the linear trapezoidal rule.

RESULTS

The patients treated in the pivotal trial were of mean (SD) age 43.7 (11.6) years and mean (SD) weight 67 (11) kg. The age range was from 18 to 70 years. Ninety seven (97) % were Caucasian females. Of the patients 51% underwent treatment for spider veins and 49% for reticular veins.

Median Number of Spider and Reticular Veins Treated during Visits

Treatment	Visit 1	Visit 2	Visit 3
1.0% Aethoxysklerol	7	5	5
1.0% Sodium Tetradecyl Sulfate	6	4.5	5
Placebo	6	6	5
0.5% Aethoxysklerol	10	8	8
1.0% Sodium Tetradecyl Sulfate	10	6	5
Placebo	11	10	6.5

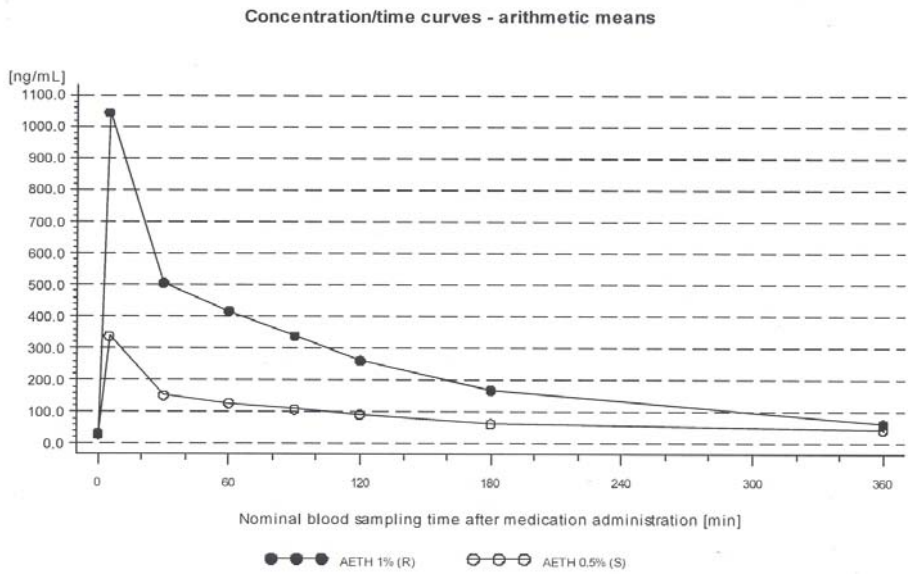
Median Doses of Aethoxysklerol and Sodium Tetradecyl Sulfate Injected into Spider and Reticular Veins Treated during Visits 1-3

	Dose, mg		
Treatment	Visit 1	Visit 2	Visit 3
1.0% Aethoxysklerol	15	8	8
1.0% Sodium Tetradecyl Sulfate	14	4	5
0.5% Aethoxysklerol	4.5	4.5	2.5
1.0% Sodium Tetradecyl Sulfate	10	4	3

The results indicate significant repeat treatment of the spider and reticular veins initially selected for treatment.

PK

Linear and semi-logarithmic plots of the arithmetic mean plasma concentrations of polidocanol, the individual plasma concentrations measured in the subjects after injection of different volumes of aethoxysklerol 0.5% and 1% solutions and the calculated PK parameters are shown in the respective figures and tables below:



14.3.1.1 Concentration/time data: Plasma concentration of Polidocanol

Plasma concentration of Polidocanol [ng/mL] as reported from analytical laboratory

Treatment	Strata	ScrNo	RanNo	0h	5min	0.5h	1h	1.5h	2h	3h	6h	*	Extra PK blood sample at least 1 week after the last varicose vein injection
AETH 1% (R)	Group R	2002	701								(b) (4)		< 10.0
		2024	704										< 10.0
		2026	714										< 10.0
		2029	716										< 10.0
		2035	713										< 10.0
		2042	717										< 10.0
		2043	715										< 10.0
		2047	718										< 10.0
		2051	720										< 10.0
		2052	719										< 10.0
AETH 0.5% (S)	Group S	2012	603										< 10.0
		2013	604										< 10.0
		2014	605										< 10.0
		2021	607										
		2022	606										< 10.0
		2028	615										< 10.0
		2032	614										< 10.0
		2036	613										
		2037	618										< 10.0
		2040	617										< 10.0
		2041	616									145.6	< 10.0
		2049	619										< 10.0

* Additional Sample: 'BLOOD FROM SEVERAL PUNCTURES BETWEEN 10:21 (+5min) AND 10:30 (+14min) HAS BEEN POOLED AND SENT TO LAB'

Stratum	RanNo	Cmax (ng/ml)	Tmax (min)	Cmax/D[1] (ng/ml/mg)	Lambda z (1/min)	thalf (min)	$AUC_{(0\text{-tlast})}$ (min*ng/ml)	$AUC_{(0\text{-inf})}$ (min*ng/ml)	$AUC_{(0\text{-inf})}/D^2$ (min*ng/ml/mg)	AUC res (%)
Group S	603	121.3	5.0	30.33	0.0108	64.38	10938.99	12555.17	3138.79	12.87
	604	106.4	5.0	23.64	0.0112	62.04	8321.40	9896.58	2199.24	15.92
	605	116.0	5.0	58.00	0.0012	577.86	10397.12	50329.96	25164.98	79.34
	606	286.9	5.0	63.76	0.0017	397.37	33804.97	69978.84	15550.85	51.69
	607	250.2	5.0	71.49	0.0032	217.58	32571.74	46509.06	13288.30	29.97
	613	136.4	5.0	54.56	0.0028	248.79	23022.51	39784.32	15913.73	42.13
	614	136.1	6.0	38.89	0.0032	216.11	24525.23	37932.09	10837.74	35.34
	615	239.9	5.0	79.97	0.0025	279.20	29712.12	50174.16	16724.72	40.78
	616	145.6	4.5	97.07	0.0012	565.75	18273.89	55900.81	37267.20	67.31
	617	1348.7	5.0	168.59	0.0054	128.44	64143.66	75169.03	9396.13	14.67
	618	691.2	5.0	86.40	0.0033	209.61	72472.93	101866.43	12733.30	28.85
	619	544.0	5.0	60.44	0.0051	137.04	49305.50	58439.76	6493.31	15.63
	N	12	12	12	12	12	12	12	12	12
	Mean	343.56	5.04	69.427	0.00429	258.680	31457.505	50711.350	14059.025	36.209
	SD	366.38	0.33	38.165	0.00338	173.206	20827.956	25397.669	9659.428	21.450
	Min	106.4	4.5	23.64	0.0012	62.04	8321.40	9896.58	2199.24	12.87
	Median	192.75	5.00	62.10	0.00320	216.85	27118.67	50252.06	13010.80	32.66
	Max	1348.7	6.0	168.59	0.0112	577.86	72472.93	101866.43	37267.20	79.34
	CV%	106.64	6.63	55.0	78.63905	67.0	66.2	50.1	68.7	59.2
	Geometric Mean	239.34	5.03	61.177	0.00335	207.175	25432.474	42871.581	10958.068	30.626

Stratum	RanNo	Cmax (ng/ml)	Tmax (min)	Cmax/D[1] (ng/ml/mg)	Lambda z (1/min)	thalf (min)	$AUC_{(0\text{-tlast})}$ (min*ng/ml)	$AUC_{(0\text{-inf})}$ (min*ng/ml)	$AUC_{(0\text{-inf})}/D^2$ (min*ng/ml/mg)	AUC res (%)
Group R	701	1046.8	5.0	61.58	0.0075	93.00	68019.16	72299.14	4252.89	5.92
	704	989.5	5.0	52.08	0.0060	116.43	87612.87	100379.36	5283.12	12.72
	713	839.5	5.0	46.64	0.0083	83.68	82062.17	86673.76	4815.21	5.32
	714	816.2	5.0	51.01	0.0112	61.76	41046.45	46864.61	2929.04	12.41
	715	489.5	5.0	37.65	0.0052	133.05	55904.52	66826.16	5140.47	16.34
	716	1980.1	5.0	110.01	0.0055	127.09	159423.48	182672.10	10148.45	12.73
	717	1345.0	5.0	67.25	0.0049	141.33	119462.49	140565.52	7028.28	15.01
	718	797.1	8.0	39.86	0.0057	121.10	103409.88	118365.28	5918.26	12.63
	719	1418.2	5.0	70.91	0.0054	128.23	68355.72	76699.13	3834.96	10.88
	720	734.9	5.0	40.83	0.0050	139.98	83491.59	98032.20	5446.23	14.83
	N	10	10	10	10	10	10	10	10	10
	Mean	1045.68	5.30	57.781	0.00646	114.565	86878.833	98937.725	5479.691	11.880
	SD	430.44	0.95	21.654	0.00201	26.460	33979.924	39751.984	1991.654	3.656
	Min	489.5	5.0	37.65	0.0049	61.76	41046.45	46864.61	2929.04	5.32
	Median	914.50	5.00	51.55	0.00559	124.09	82776.88	92352.98	5211.80	12.68
	Max	1980.1	8.0	110.01	0.0112	141.33	159423.48	182672.10	10148.45	16.34
	CV%	41.16	17.90	37.5	31.05628	23.1	39.1	40.2	36.3	30.8
	Geometric Mean	974.03	5.24	54.822	0.00623	111.261	81298.553	92329.210	5196.630	11.222

The doses of polidocanol administered with the 0.5% aethoxysklerol solution ranged between 1.5 and 9.0 mg and the doses administered with 1% aethoxysklerol solution ranged between 13 and 20 mg. The maximum dose to be administered per treatment session with aethoxysklerol 0.5% and 1.0% was to be 24 mg.

The plasma concentrations of polidocanol measured by the sponsor showed the following anomalies. The pre-dose plasma concentrations of polidocanol in 9 of 12 subjects with spider veins receiving the lower dose ranged between 35.1 ng/mL and 59.2 ng/mL (LLOQ<10 ng/mL). The pre-dose plasma concentrations in 7 of 10 subjects with reticular veins receiving the higher dose ranged between 36.5 and 47.5 ng/mL. In the remainder 3 subjects in both groups the pre-dose plasma concentrations were < LLOQ (10 ng/mL). The concentrations of the pre-dose samples were 2 to 67% of Cmax. In one subject (603)

with a positive pre-dose plasma concentration the 6 h plasma concentration was < LLOQ and in another subject (615) the 6 h plasma concentration was slightly below the positive pre-dose plasma concentration. The plasma concentrations of polidocanol were < LLOQ in all 10 subjects with reticular veins and in 10 of the 12 subjects with spider veins in the additional blood samples collected 1 week after the last treatment. In one subject (616) the mean value from several additional blood samples collected between 5 and 10 min after the first injection were about 3 times greater than that of the official Cmax collected 5 min after injection indicating that blood samples were not collected frequently enough in the early time period after injection of polidocanol.

The PK parameters of polidocanol calculated by the sponsor showed the following peculiarities. The apparent terminal half-life after 0.5% aethoxysklerol is twice that after 1.0% aethoxysklerol. The dose normalized Cmax and AUC0-inf after injection of 0.5% aethoxysklerol (smaller dose in mg) are greater than after injection of 1.0% aethoxysklerol (larger dose in mg). AUCextrapolated in 8 patients with spider veins exceeds 0.2 ● AUC0-inf which is inacceptable. After 1.0% aethoxysklerol AUCtlast-inf ranges between 6% and 16% of AUC0-inf. These findings indicate that the background concentrations contribute to the total concentration of apparent polidocanol throughout the 6 h period of blood collection.

The sponsor could not provide a plausible explanation for the positive pre-dose plasma concentrations found in the large majority of the subjects. As polidocanol is a constituent of many cosmetic creams, shampoos and oils the observed positive baseline values the sponsor suspected that the positive pre-dose concentrations could have been caused by systemic absorption of topically applied polidocanol. A query conducted by the sponsor showed that patients had used such products. However, the negative plasma concentrations of polidocanol in the additional blood samples taken one week after the last systemic administration of polidocanol did not support this explanation.

Given these anomalies, the Reviewer set up standards that acceptable data had to meet. Only data in subjects with pre-dose concentrations < 10 ng/mL (LLOQ) and extrapolated AUCs < 0.2 ●AUC were considered. The data of only 4 of the 22 subjects met the standards and they are listed in the below table:

PK Parameters of Polidocanol in Subjects with Negative Pre-dose Concentrations and AUCextrapolated< 0.2 AUC

	Dose	Cmax/D	AUC0-inf/D	AUCextrap.	t1/2	Vss	CL	Cmax
Subjects	mg	ng/mL/mg	ng•min/mL/mg	%	min	L	mL/min	ng/mL
Group S								
604	4.5	23.6	2199	16	62	45	455	106.4
Group R								
701	17	61.6	4253	5.9	93	27	235	1046.8
713	18	46.6	4815	5.3	84	25	208	839.5
714	16	51.0	2929	12	62	29	341	816.2

Median	16	51.0	4253	5.9	84	27	235	839.5

The values for dose normalized Cmax, and AUC0-inf and CL, Vss, t1/2 and Cmax in the 3 subjects receiving a dose between 16 and 18 mg polidocanol show reasonable agreement. In the single evaluable subject with spider veins who received a dose of 4.5 mg polidocanol, the dose normalized values for Cmax and AUC0-inf are smaller than in the 3 subjects receiving the higher polidocanol dose for the treatment of reticular veins. The apparent Cmax in the 3 patients with reticular veins ranges between 816.2 and 1046.8 ng/mL. However, with the blood sampling scheme it is possible that true Cmax was missed. The limitations in the interpretability of CL and Vss should be noted. Because of the mechanism of action of polidocanol and the local compression exerted during and after injection significant amounts of the drug may be trapped locally so that only a fraction of the administered dose may reach the systemic circulation. Therefore, t1/2 of polidocanol of about 1.5 h is the only parameter to be reported.

Efficacy

The sponsor's evaluation showed that aethoxysklerol 0.5% and 1.0% are significantly different from placebo in the primary endpoint, the 5-grade scale of improvement ($p< 0.0001$). The effect of aethoxysklerol was also statistically significantly greater than placebo with the secondary endpoints treatment success and patient satisfaction. The treatments with aethoxysklerol and sodium tetradecyl sulfate were not statistically significantly different in terms of improvement of the veins 12 weeks after the last injection.

Rationale for the Injection Solutions of 0.5% and 1% Aethoxysklerol

The concentration of polidocanol in the 1% aethoxysklerol injection solution for reticular veins is twice that of the 0.5% injection solution for spider veins. Because of the difference in diameter between spider and reticular veins the diluting effect of the blood volume in the respective veins varies significantly as shown in the below table:

Estimated Effective Polidanol Concentrations at Target in Spider and Reticular Veins of 40 mm or 80 mm Length

Vein	Diameter	Length	Injection Volume	Conc.	Blood Volume	Injection Solution Diluted to	Effective Co
	mm	mm	mL	mg/mL	mL	%	mg/mL
S	0.80	40	0.100	0.5	0.0201	83	0.42
		40	0.300	0.5	0.0201	94	0.47
		80	0.100	0.5	0.0402	71	0.36
		80	0.300	0.5	0.0402	88	0.44
R	2.0	40	0.100	1.0	0.126	44	0.44
		40	0.300	1.0	0.126	70	0.70

		80	0.100	1.0	0.252	28	0.28
		80	0.300	1.0	0.252	54	0.54
	3.0	80	0.100	1.0	0.567	15	0.15
		80	0.300	1.0	0.567	35	0.35

The injected volume of aethoxysklerol is not significantly diluted by the blood volume residing in spider veins so that injected and actual concentrations are nearly identical. This contrasts with the condition in reticular veins. The dilution of the injected volumes of aethoxysklerol in larger reticular veins of 2 and 3 mm diameter can be significant so that the actual concentrations are significantly smaller than those in spider veins. This may result in sub-therapeutic concentrations in reticular veins and may in part explain why repeat injections at subsequent visits were necessary in the EASI trial.

Safety

The treatments with aethoxysklerol 0.5% and 1% were safe and-apart from local symptoms at the injection site-well tolerated.

Conclusions

The bioavailability study conducted by the sponsor shows 2 major deficiencies: 1) The dose levels tested were significantly lower than the maximum dose proposed by the sponsor for a treatment day/session. Hence, the exposure of polidocanol in patients under real treatment conditions remains unknown. 2) Information obtained in the bioavailability study using substantially lower dose levels is very limited. The data in only 4 of the 22 subjects met standard acceptability criteria. The blood sampling schedule did not capture true Cmax. Even though polidocanol is an intravenously administered drug the fraction of the dose systemically available may be significantly smaller than 1.0 because of local entrapment caused by polidocanol's mechanism of action and the compression exerted during injection. Thus, the interpretation of clearance and volume of distribution is limited. The only reliable parameter is the mean t1/2 obtained in the 4 patients with acceptable data.

It is unlikely that the results of a repeat bioavailability study using the appropriate dose level of polidocanol would meaningfully increase the understanding of the safety of polidocanol in humans. Thus, a repetition of the bioavailability study is not warranted.

Comments

The clinical safety data base up to including maximum doses of 120 mg of polidocanol appears to be clean. Reportedly, maximum doses in excess of 120 mg for a treatment session/day are in European labels. An experiment performed in animals comparing the AUC of the drug after administration into a small vein while exerting compression and after intravenous administration into a large vein without compression would allow determination of the fraction of the dose of polidocanol escaping into the general

circulation. If the result of such a study is applicable to humans interpretation of observed CL and V values in humans is possible.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1%/ (b) (4)

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

/s/

PETER H HINDERLING
11/25/2009

RAJANIKANTH MADABUSHI
11/25/2009

Clinical Pharmacology/Biopharmaceutics Review

NDA	21-201
Submission Dates	9/29/2003, 12/5/2003, 12/9/2003, 12/22/2003, 2/9/2004, and 3/8/2004
Brand Name	Aethoxysklerol
Generic Name	Polidocanol
Reviewer	Lei Zhang, Ph.D.
Team Leader	Dennis Bashaw, Pharm. D.
OCPB Division	DPE III
ORM Division	DDDDP (HFD-540)
Applicant	Chemische Fabrik Kreussler & Co., GmbH
Relevant IND	IND 35,139
Type of Submission; Code	505 (b)(1); 1S
Formulation; Strength(s)	0.5%, 1%, (b)(4)
Indication	Treatment of varicose veins of the lower extremities

Addendum to NDA 21-201 Review

The Clinical Pharmacology and Biopharmaceutics review for NDA 21-201 was entered in DFS on July 9, 2004 when the final report from the Division of Scientific Investigation (DSI) was pending. This Addendum to our review on July 9, 2004 is in response to the final report we received from Dr. Subramaniam of DSI on July 16, 2004.

In the memo, Dr. Subramaniam summarizes major flaws identified in the execution of the pivotal PK study, ASK-00-01-00, and analysis of PK samples (see attached copy of findings). Based on the findings of DSI inspection of this study, it is our opinion that the data contained in ASK-00-01-00 can no longer be considered valid to support this NDA. As this study did not meet the regulatory standards for a well controlled trial, it cannot be used to meet the *in vivo* bioavailability requirement under 21CFR320 for this application. A new *in vivo* bioavailability study is needed.

Recommendation

From a Clinical Pharmacology and Biopharmaceutics perspective this application is not acceptable. The Sponsor needs to conduct a new *in vivo* bioavailability study with the to-be-marketed formulation of Aethoxysklerol in sufficient numbers of patients. Prior to initiating such a study the sponsor should meet with the FDA to review the findings of the Division of Scientific Investigation. This recommendation supercedes our previous recommendation in the NDA review on July 9, 2004.

_____

Lei Zhang, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III

Concurrence: _____

E. Dennis Bashaw, Pharm. D.
Clinical Pharmacology Team Leader
Division of Pharmaceutical Evaluation III

CC: NDA 21-201; HFD-540/Div File; HFD-540/SCO/Cross;
HFD-880 (Lazor/Selen/Bashaw/L.Zhang)

Appendix. Memo from Division of Scientific Investigation.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 16, 2004

FROM: Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director – Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 21-201, Aethoxysklerol (polidocanol), 0.5%, 0.1%, (b) (4) Sponsored by Chemische Fabrik Kreussler and Company, GmbH

TO: Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)

At the request of HFD-540, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence study:

Protocol **ASK-00-01-00**: "An Examination of Plasma Concentrations of Unchanged Compounds of ASK in Patients with Varicose Vein of Lower Extremity"

The clinical and analytical portions of Protocol ASK-00-01-00 were conducted at the Department of Dermatology, Sakai Municipal Hospital, Sakai, Japan and (b) (4) respectively.

Following the inspections at Sakai Municipal Hospital (6/14-16/04) and (b) (4) (6/17-21/04), Form 483s were issued. The objectionable items and our evaluation are as follows:

Clinical Site: Sakai Municipal Hospital, Sakai, Japan

1. **Failure to maintain proper documentation with regard to source records.**

   Specifically, the source record for Subject #5 did not document the time of dosing of the subject. Since, the time of drug administration is unknown, the pharmacokinetic (PK) parameters are not reliable.

2. **Several blood draws for the 1-day, 24 hour sample time were missed.**

   The 24 hour blood-draw for Subjects #3 and #5 were delayed by 17.75 hrs and 19.33 hours, respectively. The biopharm reviewer should evaluate if AUC for Subjects #3 and #5 were estimated using the observed time for the 24-hour blood draw.

3. **Failure to establish the criteria for the actually administered dose in subjects, within the dosing range specified in the protocol.**

   Although, the protocol specified a dose range of 1.5 to 2 mg per kg body weight, there was no explicit criteria for selecting a dose within the range. For example, Subjects # 2 and #3 were administered different doses (1.71 vs 1.84 mg/kg) although they had the same body weight (49 kg). However, the inspection confirmed that the subjects in the study were dosed within the protocol defined dose range.

Analytical Site: [redacted] (b) (4)

4. **Failure to quantitate the analyte following each wash during analysis of subject plasma samples.**

   Mobile phase (i.e. wash) samples were injected following high concentration study samples at the end of every analytical runs. This was presumably to avoid carry over. These samples indicated carry-over of analyte from the preceeding sample (Exhibit 1). However, the firm did not estimate the extent of carry-over in the wash samples. More importantly, prior to injecting the next round of subject plasma study samples, the firm

failed to inject blank samples to establish the absence of carry over. Therefore, the accuracy of the subject plasma drug concentrations cannot be assured, as the extent of carry-over in the analytical runs were not determined.

5. Failure to select the appropriate quality control (QC) levels.

The calibration standards (0.05, 0.2, 0.5, 2, **5**, **20** µg/mL) and QC levels (0.2, **2** and **16** µg/mL) were not representative of the subject plasma polidocanol concentrations. Specifically, there was no QC between 2-16 µg/mL, when all Cmax concentrations and 15-33% of subject concentrations were between 4-12 µg/mL.

6. Failure to collect data in a secure manner.

Specifically, the firm failed to maintain source data in bound notebooks in a chronological sequence of data collection.

Conclusions:

Based on the above findings, DSI recommends the following:

1) The subject polidocanol concentrations in Study ASK-00-01-00 are NOT acceptable as the accuracy of the assay was not demonstrated due to sample carry-over and inappropriate QC selection (Items 4 and 5). We recommend that the subject concentration data NOT be accepted for Agency review.

2) The PK data for Subject #5 should be excluded from the study (Item 1).

After you have reviewed this memo, please append it to the original NDA submission.

Sriram Subramaniam, Ph.D.

Attachments

Final Classifications:
VAI: Sakai Municipal Hospital, Sakai, Japan
VAI: (b) (4)

cc:
HFA-224
HFD-45/RF
HFD-48/Himaya/Subramaniam(2)/CF
HFD-880/Zhang/Bashaw
HFD-540/Cross
HFR-PA2535/Hall
Draft: SS 7/13/04
Edit: CTV 7/16/04
DSI (b) (4);O:\BE\eircover\21201che.pol.doc
FACTS ID (b) (4)

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

/s/

Sriram Subramaniam
7/16/04 11:17:31 AM
PHARMACOLOGIST

Dr. Viswanathan signed the paper copy on 7/16/04. The paper copy with exhibits was faxed to Frank Cross on 7/16/04. Paper copies will be distributed to others on the cc: list.

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

/s/

Lei Zhang
7/16/04 05:05:48 PM
BIOPHARMACEUTICS

Dennis Bashaw
7/19/04 01:36:24 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 880)** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Lei Zhang, Ph.D.**			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: **7/8/2004**	Related IND No's.: **35, 139**	NDA No. **21-201**	DATE OF DOCUMENT **9/29/2003, 12/5/2003, 12/9/2003, 12/22/2003, 2/9/2004, and 3/8/2004**	ORM division **HFD-540**
NAME OF DRUG **Aethoxysklerol (Polidocanol) 0.5%, 1% (b) (4) Solution for Injection**	PRIORITY CONSIDERATION **Standard**		Date of Formal Consult: **10/10/2003**	Drug Class**: Sclerosing agent** Indication: **Treatment of varicose veins of the lower extremities**

NAME OF THE SPONSOR: [Chemische Fabrik Kreussler & Co., GmbH, D-65203 Wiesbaden, Germany]

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	X BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☐ OTHER *(SPECIFY BELOW)*: [ ]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with Name: [ ]	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox ☐ Micro ☐ Pharmacometrics ☐ Others (Check as appropriate and attach e-mail)		☐ See submission cover letter
		X OTHER *(SPECIFY BELOW)*: [Original NDA Review]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS/REVIEW FORMAT:

Reviewer's Note: This review is not written in QBR format, because many QBR questions are not relevant due to the nature of this application. To emphasize the important findings relevant to Clinical Pharmacology and Biopharmaceutics, a consult form format is used.

Background

Varicose veins of the lower extremities are a chronic circulatory condition of superficial varices that if left untreated, often result in pain, swelling, persistent itching, deep vein thrombosis, phlebitis, eczema, and ulcers of the leg. The incidence of varicose veins varies between 25% and 60%. Women suffer more often from varicose veins. Common treatments for varicose veins include the use of compression stockings, surgery, and sclerotherapy.

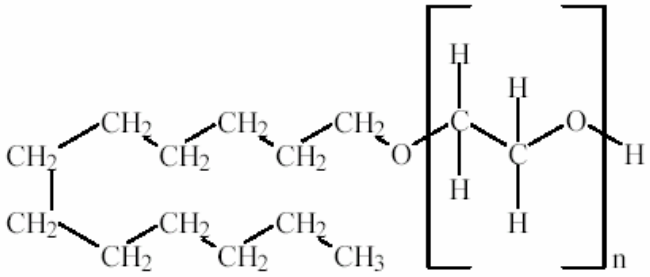
Polidocanol, the active ingredient of Aethoxysklerol® (ASK), is a "detergent" sclerosing agent, as are the FDA-approved sclerosants Sotradecol® (sodium tetradecyl sulfate) and Scleromate™ (sodium morrhuate). They act by producing venous endothelial damage (through interfering with the lipids on the cell surface) in the target vein that results in the desquamation of these cells. Subsequent intravascular reactions (vasospasm and local platelet aggregation) occlude the vein. Compression of these treated veins helps ensure the permanent transformation of the vein into fibrotic tissue. Once a vein is successfully treated by sclerotherapy, it is permanently transformed into a fibrous cord that cannot reopen. The hemodynamic effect corresponds to that achieved by the surgical removal of the varicose vein.

This NDA was originally submitted on October 1, 1999. It was withdrawn on December 1, 1999 due to incomplete pharmacokinetic data. In this new submission, the sponsor submitted a PK study report (ASK-00-01-00) to support the requirement of conducting a biostudy with to-be-marketed formulation of Aethoxysklerol. The study was conducted using the maximum strength (b) (4) (3%) in 6 patients who had primary varicose vein of lower limbs sized ≥ 3 mm in diameter and could be treated with ASK 3% at 1.5-2 mg/kg (5 were included in data analysis). The drug was also injected at the maximum (b) (4) dose (1.5 to 2 mg/kg). This PK study was considered acceptable for re-filing of this NDA.

Drug Substance and Drug Product

Drug Substance:

Polidocanol is a new molecular entity (NME). It is a mixture of homologous polymer of ethylene oxide (hydrophilic) and 1-docecanol (hydrophobic) with a corresponding molecular weight (MW) range of (b) (4) (b) (4) (mean MW ~600) (Figure 1). Chemical Formula: $C_{12}H_{25}(OCH_2\text{-}CH_2)_nOH$, n = (b) (4) (b) (4) The drug substance manufacturer for the US market will be Chemische Fabrik Kreussler, Germany.



mean extent of polymerization (n) = 9
mean molecular weight = 600

Figure 1. Polidocanol Structure.

Drug Product:

Aethoxysklerol is a sterile injection solution supplied in 2 mL ampoules in concentrations of either 0.5%, 1% (b) (4) (b) (4) concentration (Table 1). (b) (4) will be the manufacturer for the drug product

marketed in the US.

Table 1. Clinical Formulation (per 2 mL drug product).

Component	Aethoxysklerol 0.5%	Aethoxysklerol 1.0%	(b) (4)
polidocanol	10.00 mg	20.00 mg	
96% EtOH	84.00 mg	84.00 mg	
(b) (4) sodium phosphate	2.40 mg	4.80 mg	
(b) (4) potassium phosphate	0.86 mg	1.70 mg	
water for injection			
(b) (4)			

There were a series of changes in suppliers and manufacturing sites during the development of this application for Aethoxysklerol. There were three manufacturers for drug substance, polidocanol ((b) (4) (b) (4) and Kreussler) and 3 contract manufacturers of drug product, Aethoxysklerol (b) (4) (b) (4)). The drug substance used in the pivotal PK study (Study ASK-00-01-00) was manufactured by (b) (4) from Lot# 04482 and Lot# 04483. The resulting drug product (Lot # 03318) used in the Study ASK-00-01-00 was manufactured by (b) (4). Although clinical formulation composition does not change, the drug substance and the drug product used for the pivotal PK study (ASK-00-01-00) were not manufactured by the same manufacturers as the planned to-be-marketed drug substance and drug product. Because Aethoxysklerol is a solution for injection, the change in manufacturer should not result in a change in *in vivo* PK. As to the drug substance, the specifications used by (b) (4) are less rigorous than those used by Kreussler (see Appendix 2). Kreussler has additional specifications for the tests for polyethylene glycols and unidentified impurities. Therefore, the to-be-marketed drug substance would be of higher purity.

Dose-Response Relationship for Aethoxylsklerol

Aethoxysklerol is currently marketed in more than 50 countries in Europe, Asia, and South America for 3 indications (esophageal varices, hemorrhoids, and varicose veins of lower extremities) in 6 concentrations (0.25%, 0.5%, 1%, 2%, 3% and 4%).

The Sponsor submitted this NDA for marketing Aethoxysklerol (in the formulation of 0.5%, 1% (b) (4) polidocanol) in the US for the use in the lower extremities for the sclerosis of varicose veins with diameters of (b mm or less. The Sponsor proposed the following dosage recommendations for different sizes of veins (see table below):

For varicose veins ≤ 1 mm in diameter	0.1 to 0.3 mL Aethoxysklerol 0.5% per injection
For varicose veins 1 to 3 mm in diameter	0.1 to (b) (4) mL Aethoxysklerol 1% per injection
(b) (4)	

According to this proposal, a range of doses (one to several treatments) will be dosed based on size of veins and

clinical judgment for outcome. The maximum dose of polidocanol proposed is (b) (4) mg/kg per day. The dose-finding study, ASK 94-002 (conducted in Japan), appears to have been conducted after the pivotal trials (conducted in the US), therefore it is not clear how the Sponsor determined the concentrations to evaluate for safety and efficacy in Phase 3, or that the selected concentrations represent the optimal choices for the proposed indication. Therefore, dose-response relationship is not well-established for Aethoxysklerol. The doses selected are most likely based on over 20 years of clinical experience of using this drug product in patients in other countries. Please refer to Drs. Brenda Vaughan (efficacy) and Brenda Carr (safety)'s reviews for detail discussion on this topic.

Analytical Method for Study ASK-00-01-00 (the Pivotal PK Study)

The test drug ASK is an aggregate of polidocanol molecules (polyethylene glycol monododecyl ether) with different degrees of polymerization and it is difficult to identify all of its metabolites in the plasma. Only unchanged ASK was determined in this study. The analytical procedure was developed by (b) (4) (b) (4) and was transferred to (b) (4)., which conducted the assay for this study.

Because ASK is a mixture of polymers, it is impractical to monitor all the polymer species. In the assay, molecular ions with a mass-to-charge ratio (m/z) of 468.3 (degree of polymerization of polidacanol n=6), 600.5 (n=9), and 688.5 (n=11) were selected for quantitation purposes (see table below). Among them, n=9 showed higher ion intensity in the spectrum. By monitoring these three molecular ions, we could determine whether there are sequential metabolism, e.g., whether n=11 molecule will be cleaved to form n=9 molecule, etc. or whether metabolism of each molecule is parallel. From concentration data generated by monitoring these three molecules, it was found that concentration monitored by all three molecules declined with time in parallel, suggesting no or little sequential metabolism (Appendix 3, Table 3.1). PK results generated from n=9 and n=11 were comparable (Appendix 3, Table 3.2). Lower exposure results were obtained with n=6 molecules. We would not expect that concentration results generated from these 3 molecules would be identical because metabolism could be different depending on chain length. Therefore, the percentage of these ions in the mixture would change over time and concentrations of these ions would not represent concentrations of the mixture of all polymers. Therefore, PK results obtained by this analytical method could only be used to provide an estimate of the PK parameters of ASK (mixture of polymers) because we do not know which species would represent mixture of polymers. We select to show data generated from n=9 molecule in the PK section because this molecule may be a reasonable representer because of its high abundance.

Assay Method and Sample preparation	LC/MS method was used to assay unchanged polidocanol. HPLC was performed using a (b) (4)
Analytical Site	(b) (4)
Internal Standard (m/z = (b) (4))	(b) (4)
Matrix	Human plasma

Compound	Polidocanol (degree of polymerization, N=6)	Polidocanol (degree of polymerization, N=9)	Polidocanol (degree of polymerization, N=11)
Mass to charge ratio (m/z)	468.3	600.5	688.5
Standard curve range	0.05 to 20 µg/mL r > 0.994		
Sensitivity (LOQ)	0.05 µg/mL		
Accuracy (Relative Error: RE) **Intra-day**	0.0%-8.2%	0.5%-12%	-0.1%-8.0%
Inter-day	-7.3%-10%	-4.8%-0.0%	-5.7%-8.0%
Precision (CV%) **Intra-day**	1.1%-18%	3.3%-12.5%	1.8%-14.8%
Inter-day	3.6%-15.1%	4.0%-6.5%	4.6%-9.8%
Recovery	>84%	>77%	>77%
Selectivity	No interfering peaks	No interfering peaks	No interfering peaks
Stability after 3 freeze/thaw cycles	<12%		
Stability in an automatic sampler after pretreatment of samples	<10% at 48 hr		
Stability after storage at –20°C	< 20% for 5 months		
Reviewer's Comments	*Method is acceptable for the quantitation of ASK in human plasma. The stability data covered the period between sample collection and analysis (5 months).*		

Summary of Clinical Pharmacology and Biopharmaceutics Findings

The pivotal PK study, ASK-00-01-00, in this submission was not conducted by the Sponsor. This study was conducted in Japan for the evaluation of ASK to be marketed in Japan. In Study ASK-00-01-00, only 6 Japanese patients were studied and data from 5 patients (1 male and 4 females) were used for primary analysis. While this is a small number of subjects for a pivotal PK trial for an NME, it was considered acceptable given that ASK is an intravenous drug that closes blood vessels and it would be unethical to administer it to healthy volunteers. As it is an IV drug and its mode of use (clinically, it is designed to preclude systemic distribution), it was agreed upon to determine PK from a small group of patients. Due to the very limited number of patients, the effect of age, gender, and body weight on PK of ASK could not be evaluated, but again, given the disease state and conditions of use, these should not be significant factors in the clinical use of this drug.

It should be noted that the PK of ASK was not studied in a representative US population but instead in a Japanese population. In terms of a racial basis for differences in pharmacokinetics, it is known that alcohol dehydrogenase (ADH) has been shown to be responsible for the oxidation of polyethylene glycols (PEG). Because polidocanol is a derivative of PEG, it is possible that ADH, together with aldehyde dehydrogenase (ALDH), is responsible for the formation of carboxylated metabolites of polidocanol. ADH is polymorphic and that 85% of Japanese carry an atypical liver ADH that results in higher incidence of poor metabolizers in Japanese than Caucasians. If this is the case, we would expect to see lower or similar exposure in Caucasians compared to Japanese. It is not clear whether polymorphic cytochrome P450 enzymes (e.g., CYP2D6, CYP2C19) are involved in the metabolism of polidocanol. The safety and efficacy of Aethoxysklerol were studied in both Caucasian and Japanese patients, and comparable results were obtained suggesting little ethnic difference. Therefore, PK data obtained in this study appear to cover the exposure of polidocanol in general population. Additional PK studies in a representative US population are not necessary at this time.

As mentioned earlier (in analytical section), PK results obtained by LC/MS method could only be used to

provide an estimate of the PK parameters of ASK (mixture of polymers) because it is impractical to monitor all polymer species. By monitoring selected molecules, we do not know which molecule would represent mixture of polymers. Here we select to show data generated from n=9 molecule because this molecule may be a reasonable representer because it represents mean extent of polymerization.

The results from Study ASK-00-01-00 suggest that under the conditions used in this trial that there is systemic circulation of ASK with a C_{max} of 6.6 to 10.3 µg/mL reached immediately after injection (dose range 1.62-1.88 mg/kg) (based on n=9 molecule) (Table 2). ASK has a short half-life (~ 1 hr) and its blood level was less than detection limit (0.05 µg/mL) at 24 hr and beyond. Total clearance of ASK was 12.4 L/hr. The volume of distribution was 18 L (> volume of body water), indicating there is some tissue distribution of ASK. The inter-subject variability is small (CV < 30%) and is reflective of IV administration. ASK is expected to cause variceal regression by scarring vascular tissue through local injury of vascular endothelial cells. It was not clear how these exposure values (amount of ASK entering the systemic circulation) relate to systemic adverse events of ASK.

Table 2. PK Parameters of ASK (based on n=9 molecule).

	Mean ± SD	Range
Dose (mg/kg)		1.62-1.88
C_{max} (µg/mL)*	8.24 ± 1.40	6.64-10.32
$T_{1/2}$ (hr)	1.10 ± 0.15	0.94-1.27
$AUC_{0\text{-}inf}$ (µg·hr/mL)	8.38 ± 1.99	6.19-10.90
CL (L/hr)	12.41 ± 3.63	8.26-17.44
MRT (hr)	1.48 ± 0.23	1.30-1.77
Vdss (L)	17.9 ± 3.40	14.63-22.76

* Reached immediately after injection.

Because this PK study is a pivotal *in vivo* PK study to support the approval of this NDA, a consult request was made in January 2004. At the time of this review, the final report from DSI is pending.

Summary of Clinical Findings *(Please refer to Drs. Brenda Vaughan (efficacy) and Brenda Carr (safety)'s reviews for details.)*
A *Non-Approvable* recommendation is being made for the use of Aethoxysklerol (polidocanol) as a sclerosant intended for intravenous administration for treatment of ≤1 to (b) mm diameter varicosities of the lower extremities. The following was extracted from the medical officers' summary:

> *The Applicant failed to establish superiority for the dichotomized Complete Disappearance of Varicosities efficacy endpoint as proposed by the Division or Disappearance of Varicosities on a 5-point scale as proposed by the Applicant when Aethoxysklerol is compared to diluted Sotradecol (STS). It is of note that non-inferiority was also not established for the dichotomized Complete Disappearance of Varicosities efficacy endpoint. It is recommended that the application is Not-Approvable. While the submitted safety data revealed an adverse event profile consistent with sclerotherapy and the pharmacologic class of sclerosants, and raised no new safety concerns or apparent polidocanol-specific effect, efficacy was not demonstrated. Thus, the risk-benefit analysis does not favor approval.*

Safety

While no safety issues were identified during the in *vivo* pharmacokinetics trial, it should be noted that there is a real risk to the combined use of polidocanol with certain injectable anesthetic agents. Specifically, besides being a sclerosing agent, polidocanol also has local anesthetic properties. As such, it can have an additive effect with other systemically administered anesthetic agents on cardiac function, i.e., bradycardia. Treatment of varicose veins with polidocanol should be done separately from surgical treatment of varicose veins to avoid the potential for cardiac side-effects. While we have no evidence for this effect in this NDA, appropriate warning language will be developed with the medical officer for inclusion in the labeling once the application becomes approvable.

Recommendation

From a clinical pharmacology and biopharmaceutics perspective this application is acceptable. The labeling recommendation for both the Clinical Pharmacology sub-section and the warning regarding use of polidocanol concurrently with local anesthetics will be deferred at this time pending the completion of a successful clinical development program.

SIGNATURE OF REVIEWER: _Lei Zhang_____ **SIGNATURE OF TEAM LEADER:** E. Dennis Bashaw	Date _____ Date _____
CC.: HFD # [880**]; TL: [**Dennis Bashaw**]; DD: [**John Lazor]; **DDDD** [Arzu Selen]	**Project Manager: Frank Cross Date** _____

Appendix 1. Individual Study Review (Study ASK-00-01-00). (P.8)

Appendix 2. Specifications Comparison of Polidocanol Manufactured by Kreussler and [redacted]. (P. 13)

Appendix 3. PK Results Generated Using Calibration Curve for n=6, 9, and 11 Molecule. (P.14)

Appendix 4. OCPB Filing and Review Form. (P.16)

Appendix 1. Individual Study Review (Study ASK-00-01-00).

ASK-00-01-00: An Examination of Plasma Concentrations of Unchanged Compounds of Aethoxysklerol (ASK) in Patients with Varicose Vein o f Lower Extremity (Volume 27)

Study Period: July 18, 2000 to August 15, 2000
Sample Analysis Period: December 14, 2000 to December 21, 2000
Principle Investigators: Dr. Akihiro Hume and Dr. Junichi Azuma
Study Center: Department of Dermatology, Sakai Municipal Sakai Hospital, 1-1-1 Minamiyasui-cho, Sakai, 590-0064, Japan
Analytical Lab: (b) (4) (b) (4)

Objectives: To determine the plasma concentration of Aethoxysklerol (ASK) (generic name, polidocanol) in patients with varicose vein of lower extremities after administration at its clinical recommended doses.

Study Design: This was an open study designed to enroll 6 patients (who had primary varicose vein of lower limbs sized ≥ 3 mm in diameter and who could be treated with ASK 3% at 1.5-2 mg/kg) at a single center. Immediately before intravariceal injection of ASK, carbon dioxide gas was used to remove intravariceal blood and thus to prevent intravariceal thrombosis. Administration of ASK was performed at a single time through several variceal punctures (within 1 minute) to deliver the whole dose (0.5-1 mL/puncture). The plasma concentrations of unchanged ASK were determined from immediately after injection to 3 hours after administration to monitor the phase of its extravariceal efflux as well as at 1, 3 and 7 days post-dose to monitor its gradual distribution to the systemic circulation.

Subjects: A total of 6 subjects were enrolled to receive drug and 5 were included in primary PK analysis (PPS) (Table 1). All were Japanese. Patient 2 had drug allergy, one of the condition included in the exclusion criteria. Because this patient might have drug allergy, PK data from this patient were excluded from primary (PPS) analysis of plasma concentration of unchanged ASK.

Table 1. Baseline Demographic Characteristics (5 PPS Patients, 1 Male and 4 Females)

	Mean	Std	Min	Max
Age (y)	49.6	14.9	26	62
Weight (kg)	56.8	7.4	49	66

Reviewer's Comments: *In this study, only 6 Japanese subjects were enrolled. It was acceptable. ASK is an intravenous drug that closes blood vessels. Therefore it is unethical to administer it to healthy volunteers.*

Identity of Investigational Product:

Name of the test product	Dosage form	Active ingredient and its content (%)	Lot No.	Expiration date
ASK–030	Injection	Each ampule contains 60 mg of polidocanol per 2 mL (3%)	03318	February 2, 2003

Dosing Information (5 PPS Patients):

Patient No.	Needle Size	Needle Type	Dosing Volume/Puncture (mL)	No. of Injection	Total Dosing Vol (mL)	Carbon Dioxide Volume (mL)
1	23	Winged	0.9	4	3.6	4
3	23	Winged	0.6	5	3.0	5
4	23	Winged	0.85	4	3.4	6
5	23	Winged	0.8	4	3.2	6
6	23	Winged	0.8	4	3.2	6

Sample Collection and Handling:
Blood was collected at the following times: before administration (during the week before administration), immediately after (to 5 minutes after) administration, and at 15 (+5) minutes, 30 (+5) minutes, 1 (+0.1) hour, 2 (+0.2) hours, 3 (+0.3) hours, 1 day, 3 days, and 7 (+1) days after administration. The acceptable time windows are shown in parentheses.

Whole blood (5 mL each time) was collected from the left (or right) cubital vein into heparinized tubes. The blood was centrifuged to separate plasma. The plasma samples were transferred to specified (polypropylene) tubes and stored at ≤ -20ºC.

Sample Analysis: The test drug ASK is an aggregate of polidocanol molecules (polyethylene glycol monododecyl ether) with different degrees of polymerization and it is difficult to identify all of its metabolites in the plasma. Only unchanged ASK was determined in this study. The analytical procedure was developed by (b) (4). and was transferred to (b) (4) which conducted the assay for this study.

LC/MS method was used to assay unchanged polidocanol. (b) (4) The peak area ratio observed with each sample was used to back-calculate the concentration of each analyte from the calibration curve.

(b) (4) was used as an internal standard. Because ASK is a mixture of polymers, it is impractical to monitor all the species. In the assay, molecular ions with a mass-to-charge ratio (m/z) of 468.3 (degree of polymerization of polidacanol n=6), 600.5 (n=9), and 688.5 (n=11) were selected for quantitation (Table 2). Among them, n=9 showed higher ion intensity in the spectrum. The detection limit was (b) (4) µg/mL. The details of analytical method and its validation (Study No. SBL 62-77 and SBL 62-78) are included in Volume 27, Appendix. 16.1.5.

Table 2. Molecular Ion Monitored.

Compounds	Q1 (m/Z*)
Polidocanol (degree of polymerization n=6)	468.3
Polidocanol (degree of polymerization n=9)	600.5
Polidocanol (degree of polymerization n=11)	688.5
Internal standard	(b) (4)

*: mass-to-charge ratio

Pharmacokinetic and Statistical Analysis: The following PK parameters were calculated using a nonparametric method: $AUC_{0-\infty}$, $t_{1/2}$, CL_{tot}, $MRT_{0-\infty}$, and Vdss. C_{max} was the maximum concentration observed and T_{max} was the time when the maximum concentration was reached.

Pharmacokinetic Results:
Plasma ASK concentration declined over time (Table 3 and Figure 1). It was below detection limit (b) (4) µg/mL) at Days 1, 3 and 7. Only data from quantitation of n=9 molecule, the one with the highest ion intensity, were listed. We would not expect that concentration results generated from these 3 molecules would be identical because metabolism could be different depending on chain length. Therefore, percentage of these ions in the mixture would change over time and concentrations of these ions would not represent concentrations of the mixture of all polymers. As a result, PK results generated from n=9 and n=11 were comparable (Appendix 3). Lower exposure results were obtained with n=6 molecules. Therefore, PK results obtained by this analytical method could only be used to provide an estimate of the PK parameters of ASK (mixture of polymers) because we do not know which species would represent mixture of polymers. We select to show data generated from n=9 molecule in the PK section because this molecule may be a reasonable representer because of its high abundance.

C_{max} was reached immediately after injection with a level of 6.6 to 10.3 µg/mL among 5 patients. The half-life of ASK is short (~ 1 hr) (Table 4). Because no plasma samples were collected between 3 and 24 hr, whether this half-life represents elimination half-life is unknown. However, this half-life is similar to MRT (mean 1.5 hr), suggesting that it represents the effective half-life of ASK. Total clearance was 12.4 L/hr. The volume of distribution was 18 L (> volume of body water), indicating there are tissue distribution for ASK.

Table 3. Plasma Concentrations of Unchanged ASK Over Time in the 5 PPS Patients (based on n=9 molecule).

Patient No.	Plasma concentration of unchanged ASK (µg/mL)								
	Immediately after administration	15min	30min	1h	2h	3h	1day	3day	7day
1	(b) (4)						ND	ND	ND
3							ND	ND	ND
4							ND	ND	ND
5							ND	ND	ND
6							ND	ND	ND
Min							ND	ND	ND
Max							ND	ND	ND

ND: Below the Detection Limit ((b) (4) µg/mL).

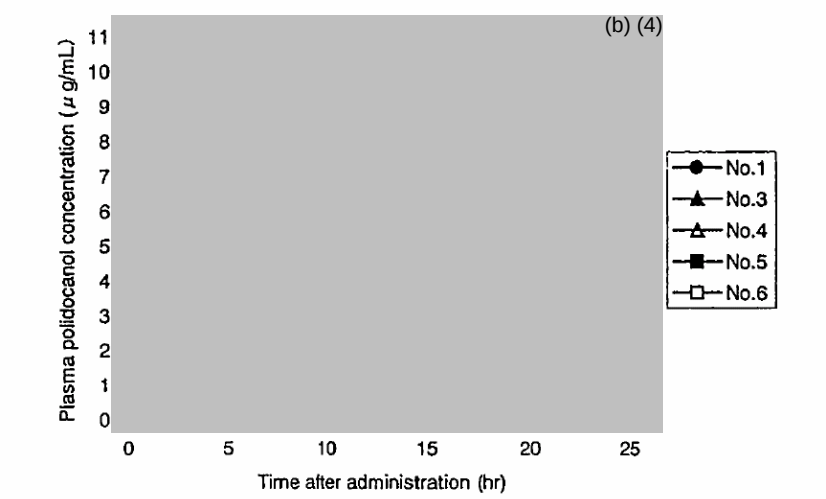


Figure1. Plasma Concentration of Unchanged ASK Over Time in the 5 PPS Patients.

Table 4. PK Parameters of ASK (based on n=9 molecule).

	Mean ± SD	Range
Dose (mg/kg)		1.62-1.88
C_{max} (μg/mL)*	8.24 ± 1.40	6.64-10.32
$T_{1/2}$ (hr)	1.10 ± 0.15	0.94-1.27
$AUC_{0\text{-}inf}$ (μg·hr/mL)	8.38 ± 1.99	6.19-10.90
CL (L/hr)	12.41 ± 3.63	8.26-17.44
MRT (hr)	1.48 ± 0.23	1.30-1.77
Vdss (L)	17.9 ± 3.40	14.63-22.76

* Reached immediately after injection.

Comparison to the Historical Data:
In Study 1187015-BBP, single dose PK of ASK was studied in male healthy subjects after IV injection of ^{14}C-polidocanol. Because documentation for the validation of the methods used in this study is not available, the results are not reviewed. In this old study, ASK was assayed with liquid scintillation so all ASK species (include metabolites) were monitored. PK parameters of ASK were found to be: CL 11.7 L/hr, elimination half-life 4.1 hr and Vd 24.5 L. 89% of the administered dose of ASK was eliminated from blood within 12 hr, and it was eliminated by both renal and biliary routes. The mean protein binding was 59% at 1 hr after administration.

The PK parameters (based on n=9 molecule) obtained in this study were very similar to the historical study although patients and intravariceal injection were used in the new study. The similar plasma kinetics of ASK in patient population to that in healthy individuals might be related to the injection sclerotherapy procedure that facilitates drug distribution into systemic circulation, i.e., compression of the injection site by a compress and by an elastic bandage followed by increased physical activity for preventing deep venous thrombosis.

Summary: PK data from Study ASK-00-01-00, conducted in patients with varicose veins of lower extremities at the highest dose and maximum concentration indicated in the draft labeling, suggested that there is systemic circulation of ASK with a C_{max} of 6.6 to 10.3 μg/mL reached immediately after injection (based on n=9 molecule). ASK had a short half-life (~ 1hr) and its level was less than 0.05 μg/mL at 24 hr and beyond. Total clearance of ASK was 12.4 L/hr. The volume of distribution was 18 L, indicating there are tissue distribution for

ASK. ASK is expected to cause variceal regression by scarring vascular tissue through local injury of vascular endothelial cells. It was not clear how these exposure values (amount of ASK entering the systemic circulation) relate to systemic adverse events of ASK. Safety needs to be closely monitored.

Due to limit number of patients, effect of age, gender, body weight on PK of ASK was not evaluated.

1 Page(s) has been Withheld in Full immediately following this page as B4 (CCI/TS)

Appendix 3. PK Results Using Calibration Curve Generated for n=6, 9, and 11 Molecule.

Table 3.1

Table 1 Concentrations of polidocanol in human plasma

		Concentration (μg/mL)		
		n=6	n=9	n=11
Subject No.	Time(h)	(468.3m/z)	(600.5m/z)	(688.5m/z)
1	Pre			(b) (4)
1	0			
1	0.25			
1	0.5			
1	1			
1	2			
1	3			
1	24			
1	72			
1	168			
2	Pre			(b) (4)
2	0			
2	0.25			
2	0.5			
2	1			
2	2			
2	3			
2	24			
2	72			
2	168			
3	Pre			
3	0			
3	0.25			
3	0.5			
3	1			
3	2			
3	3			
3	24			
3	72			
3	168			
4	Pre			
4	0			
4	0.25			
4	0.5			
4	1			
4	2			
4	3			
4	24			
4	72			
4	168			
5	Pre			
5	0			
5	0.25			
5	0.5			
5	1			
5	2			
5	3			
5	24			
5	72			
5	168			
6	Pre			
6	0			
6	0.25			
6	0.5			
6	1			
6	2			
6	3			
6	24			
6	72			
6	168			

N.D. : below the limit of quantitation ((b) g/mL)

Table 3.2

Table: Pharmacokinetic parameters calculated by a nonparametric method

(using a calibration curve generated for the n=6 molecule)

Patient No.	C_{max} (μg/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (hr·μg/mL)	$MRT_{0-\infty}$ (hr)	Cl_{tot} (L/hr)	Vd_{ss} (L)	Remarks
1	6.469	0.08	1.322	5.334	1.728	20.25	34.99	
3	6.236	0.02	1.077	5.051	1.443	17.82	25.71	
4	7.225	0.00	1.071	4.665	1.276	21.86	27.90	
5	8.923	0.02	0.934	4.028	1.016	23.83	24.20	
6	4.741	0.00	1.125	4.980	1.362	19.28	26.24	
2	5.608	0.00	1.147	3.746	1.310	22.43	29.38	Patient excluded from primary analysis

(using a calibration curve generated for the n=9 molecule)

Patient No.	C_{max} (μg/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (hr·μg/mL)	$MRT_{0-\infty}$ (hr)	Cl_{tot} (L/hr)	Vd_{ss} (L)	Remarks
1	7.292	0.08	0.936	6.193	1.305	17.44	22.76	
3	8.549	0.02	1.273	10.898	1.772	8.26	14.63	
4	8.388	0.00	1.208	8.319	1.610	12.26	19.74	
5	10.319	0.02	0.956	6.721	1.198	14.28	17.10	
6	6.645	0.00	1.155	9.778	1.538	9.82	15.10	
2	6.365	0.00	1.077	6.563	1.429	12.80	18.29	Patient excluded from primary analysis

(using a calibration curve generated for the n=11 molecule)

Patient No.	C_{max} (μg/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (hr·μg/mL)	$MRT_{0-\infty}$ (hr)	Cl_{tot} (L/hr)	Vd_{ss} (L)	Remarks
1	7.883	0.08	0.881	5.656	1.206	19.09	23.02	
3	10.043	0.02	1.139	10.025	1.504	8.98	13.50	
4	10.556	0.00	1.195	7.674	1.479	13.29	19.65	
5	12.545	0.02	0.991	6.857	1.154	14.00	16.15	
6	8.408	0.00	1.037	9.303	1.359	10.32	14.02	
2	7.961	0.00	0.983	6.165	1.247	13.63	16.99	Patient excluded from primary analysis

Appendix 4. OCPB Filing and Review From.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-201**	**Brand Name**	**Aethoxysklerol**
OCPB Division (I, II, III)	**DPE III (HFD-880)**	**Generic Name**	**Polidocanol**
Medical Division	**DDDDP (HFD-540)**	**Drug Class**	**Sclerosing agent**
OCPB Reviewer	**Lei Zhang, Ph.D.**	**Indication(s)**	**Treatment of varicose veins of the lower extremities**
OCPB Team Leader	**Dennis Bashaw, Pharm. D.**	**Dosage Form**	**0.5%, 1%, (b)**
		Dosing Regimen	**For varicose veins ≤ 1 mm in diameter: 0.1 to 0.3 mL Aethoxysklerol 0.5% per injection** **For varicose veins (b) 1 to 3 mm in diameter: 0.1 to (b) mL Aethoxysklerol 1% per injection** (b) (4) **Not to exceed (mg polidocanol per kg per day.**
Date of Submission	**9/29/2003**	**Route of Administration**	**Intravenous**
Estimated Due Date of OCPB Review	**6/1/2004**	**Sponsor**	**Chemische Fabrik Kreussler & Co., GmbH**
PDUFA Due Date	**8/2/2004**	**Priority Classification**	**New Molecular Entity (1-S)**
Division Due Date			**IND 35,139**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
Human PK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**Study 1187015-BBP (not an acceptable study because of lack of documentation)**
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**X**	**1**	**1**	**Study ASK-00-01-00**
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			
Total Number of Studies		**2**	**1**	

Filability and QBR comments

	"X" if yes	Comments
Application filable?	X	
Comments sent to firm?	X	• **Please provide the source and identification information of the drug substance and the dosage form used in the pivotal PK study, ASK-00-01-00; and confirm whether they are the same as the to-be-marketed drug substance and dosage form.** • **Please submit the clinical study report for ASK-00-01-00 in an electronic format if available.**
QBR questions (key issues to be considered)	• **What is the systemic exposure (and PK profile) of polidocanol under the conditions that mimic the maximal doses to patients following inadvertent systemic administration?** • **Was the drug substance and dosage form used in PK studies the same as the intend-to-be-marketed drug substance and dosage form?**	
Other comments or information not included above	**Due to a series of changes in suppliers and manufacturing sites, it was not clear whether the drug substance and the final dosage form used for the pivotal PK study were the same as the planned to-be-marketed drug substance and dosage form. The sponsor will provide a statement of the lots of the drug substance used in the PK study (the drug substance was manufactured by an earlier manufacturer). The sponsor will provide a statement of the specifications for the raw drug substance used in the PK study and to-be-marketed drug substance (impurity profile, etc.) and confirm that they are identical.**	
Primary reviewer Signature and Date	**Lei Zhang**	
Secondary reviewer Signature and Date	**Dennis Bashaw**	

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

/s/

Lei Zhang
7/9/04 11:55:45 AM
BIOPHARMACEUTICS

Dennis Bashaw
7/12/04 02:27:31 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-201	Submission Date: 9/29/2003
Brand Name	Aethoxysklerol
Generic Name	Polidocanol
Reviewer	Lei Zhang, Ph.D.
Team Leader	Dennis Bashaw, Pharm. D.
OCPB Division	DPE III
ORM Division	DDDDP (HFD-540)
Applicant	Chemische Fabrik Kreussler & Co., GmbH
Relevant IND	IND 35,139
Type of Submission; Code	505 (b)(1); 1S
Formulation; Strength(s)	0.5%, 1%, (b) (4)
Indication	Treatment of varicose veins of the lower extremities

NDA 21-201 Filing Memo

This NDA was originally submitted on October 1, 1999. It was withdrawn on December 1, 1999 due to incomplete Pharmacokinetic data. In this new submission, the sponsor submitted a PK study report (ASK-00-01-00) to support the requirement of conducting a biostudy with the to-be-marketed formulation of Aethoxysklerol. The study was conducted using the maximum strength of the (b) (4) (3%) in 6 patients (5 were included in data analysis). The drug was also injected at the maximum dose (1.5 to 2 mg/kg). However, due to a series of changes in suppliers and manufacturing sites, it was not clear whether the drug substance and the final dosage form used for this pivotal PK study were the same as the planned to-be-marketed drug substance and dosage form. Provided this issue can be clarified, then the Clinical Pharmacology and Biopharmaceutics section of this NDA application is acceptable for filing.

Comments

1. Please provide the source and identification information of the drug substance and the dosage form used in the pivotal PK study ASK-00-01-00. And confirm whether they are the same as the to-be-marketed drug substance and dosage form.
2. Please submit the clinical study report for ASK-00-01-00 in an electronic format if available.

Recommendation

If the question of what drug substance and final dosage form were used in the pivotal PK study is addressed appropriately, the Clinical Pharmacology and Biopharmaceutics section of this NDA application is acceptable for filing. Please convey the above comments to the sponsor.

_____

Lei Zhang, Ph.D.
PK Reviewer
Division of Pharmaceutical Evaluation III

Concurrence: _____

E. Dennis Bashaw, Pharm. D.
Team Leader
Division of Pharmaceutical Evaluation III

CC: NDA 21-201; HFD-540/Div File; HFD-550/RPM/Carrington;
HFD-880 (Lazor/Bashaw/L.Zhang)

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

/s/

Lei Zhang
11/26/03 12:14:25 PM
BIOPHARMACEUTICS

Dennis Bashaw
11/28/03 10:05:08 AM
BIOPHARMACEUTICS