CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-201s000

OTHER REVIEW(S)

Project Manager Overview

NDA 021201 Asclera (polidocanol) 0.5% and 1% injection

Background:

This NDA was initially submitted to the Division of Dermatologic and Dental Drugs DDDD on October 1, 1999 but was withdrawn December 1, 1999. The application was resubmitted on October 2, 2003 and filed on December 1, 2003. After review DDDD notified the sponsor that the application was Not Approvable on August 2, 2004. In May of 2005 this NDA was transferred to the Division of Cardiovascular and Renal Products DCRP. On July 21, 2008 the sponsor resubmitted their NDA to DCRP. After review this submission was determined to be an Incomplete Response by DCRP. The sponsor was notified of this determination on August 18, 2008. The sponsor resubmitted their NDA to DCRP on July 10, 2009, this submission is the subject of the current review cycle.

NDA Reviews and Memos

Office Director's Memo

Dr. Robert Temple; March 30, 2010

In his memo Dr. Temple has the following conclusion; polidocanol 0.5 and 1% should be approved for treatment of small varices (spider veins and reticular veins) with limited doses and a bolded warning about use of larger doses and injection of larger veins. The sponsor will communicate these concerns to physicians and remind them of the need to have provisions for dealing with allergic reactions. The rates of serious allergic/anaphylactic reactions in long-standing foreign use and with US marketed Sotradecol are so low that a Boxed Warning or Medguide do not appear warranted.

Division Director's Memo

Dr. Norman Stockbridge; December 22, 2009

In his memo Dr. Stockbridge recommends to approve Asclera (polidocanol) to sclerose spider and reticular veins. Dr. Stockbridge comments that on the issue of anaphylaxis, the review team has the impression that this risk may increase with dose. Dr. Stockbridge comments that a goal of labeling and any additional post-marketing safety-related activities ought to be to discourage offlabel use for larger varicosities where the volume of drug necessary will be much higher than it is for the indicated uses.

Deputy Division Director's Memo

Dr. Mary-Ross Southworth; December 17, 2009

In her review Dr. Southworth recommends that labeling include a warning describing cases of severe allergic reactions including anaphylaxis, cardiac arrest, and death. She comments that a boxed warning might be considered but that this decision warrants further discussion.

She also recommends requiring, as part of approval, a Risk Evaluation and Mitigation Strategy (REMS) that would include a Communication Plan to physicians for a finite period after approval describing the risk associated with polidocanol and directing the prescribers to limit the volume administered, have emergency equipment available, and to not readminister in patients displaying signs of hypersensitivity.

Dr. Southworth comments that a Medication Guide could be considered as well, though, practically, this drug will be dispensed by the physician administering the drug and discussions of the risk/benefit would take place prior to administering the drug, in the office or practice setting.

Dr. Southworth comments that Elements to assure safe use (restricted distribution) are not necessary as this product is intended to be administered by physicians in their practice settings.

CDTL Memo Dr. Khin Maung U; December 18, 2009 Recommended Action: Approval See review for details.

Clinical Review; Novmeber 16, 2009 Dr. Khin Maung U Recommended Action: Approvable

In his review Dr. U concludes that this application is approvable, pending the sponsor's response to comply with his recommendations in section 9.2 (page 55) of his review describing changes to (1) Indications and Usage, (2) Dose Considerations, (3) Contraindications and (4) Warnings and Precautions of the proposed labeling.

Statistical Review; November 25, 2009 Dr. John Lawrence

Dr. Lawrence filed a joint Clinical/Statistical review, concurring with Dr. U.

Clinical Pharmacology; November 25, 2009

Dr. Peter Hinderling

Dr. Hinderling's review had the following summary and recommendation:

Summary: 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.

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.

Pharmacology Review; November 18, 2009 Dr. Tim Link Recommended action: Approvable Please see review for details.

Chemistry Review; March 18, 2010 Dr. Wendy Wilson Recommended action: Approval

Microbiology Review; December 21, 2009, Dr. Vinayak Pawar Recommended action: Approval In his review as amended December 21, 2009, Dr. Pawar recommends approval. Please see review for more details.

Action Items:

An approval letter will be drafted for Dr. Temple's signature.

by Michael Monteleone March 30, 2010

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

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/s/

MICHAEL V MONTELEONE 04/01/2010

Evaluation ond Research Lannon - FDA - H	Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology
Date:	January 7, 2010
To:	Norman Stockbridge, M.D Division of Cardiovascular and Renal Products
Through:	Laura Pincock, PharmD, Acting Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Shirley Zeigler, MSN, CRNP, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Asclera (Polidocanol) Injection 0.5% (10 mg/2 mL) and 1% (20 mg/2 mL)
Application Type/Number:	NDA 21201
Applicant:	Chemische Fabrik Kreussler & Co., GmbH
OSE RCM #:	2009-2241

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2	METHODS AND MATERIALS	. 3
3	RECOMMENDATIONS	. 3
	3.1 Comments to the Division	.3
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1 INTRODUCTION

This review is written in response to a request from the Division of Cardiovascular and Renal Products for assessment of labels and labeling for Polidocanol Injection. At the request of the OND Regulatory Project Manager, the Division of Medication Error Prevention and Analysis (DMEPA) forwarded our recommendations on the container labels and carton labeling to the Division in an e-mail dated December 15, 2009 (see Appendix A).

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) to evaluate the container labels and carton labeling submitted on November 13, 2009, December 8, 2009 and December 23, 2009, and the insert labeling submitted on November 13, 2009 (Appendices B through M).

3 RECOMMENDATIONS

Our evaluation noted areas where information on the label and labeling can be clarified and improved on to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1, *Comments to the Division*.

The Applicant's December 23, 2009 submission addressed all of DMEPA's concerns on the container labels and carton labeling as listed in Appendix A.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Nina Ton, OSE Regulatory Project Manager, at 301-796-1648.

3.1 COMMENTS TO THE DIVISION

A. Insert Labeling

- 1. Modify the word "ampoule" to read "ampule" for the correct American-English spelling.
- In the DOSAGE FORMS AND STRENGTH, revise the strengths to read as "0.5% (10 mg/2 mL) and 1% (20 mg/2 mL)" solution in 2 mL glass ampules to maintain consistency with the container label and carton labeling.

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

APPENDICES

APPENDIX A:

COMMENTS TO THE APPLICANT

A. Container Label

- 1. The abbreviation "IV" should be spelled out as "Intravenous" on all of the labels and labeling to reduce the potential for misinterpretation of the abbreviation.
- 2. Replace the statement ^{(b) (4)} on the principal display panel with the statement "Single use: Discard unused portion".
- 3. Remove the swoosh line between the proprietary name and the established name on the container label. There should be no intervening matter that appears between the proprietary name and the established name to comply with 21 CFR 201.10(a).
- 4. Ensure the established name is at least ½ the size and prominence of the proprietary name to comply with 21 CFR 201.10(g)(2). The proprietary name, established name, and strength should be the most prominent information communicated on the principal display panel.
- 5. The presentation of strength on the container label, "0.5%", is difficult to read as currently printed in white font inside the gray circular-shaped graphic. Revise the white font color to another prominent color to provide adequate contrast, thereby increasing the prominence of the strength.
- 6. Increase the font size of the circular graphics conveying the strength (0.5% and 1%) to improve readability on the small vial.
- 7. Modify the word "ampoule" to read "ampule" for the correct American-English spelling.
- 8. Revise the unit "ml" to read as "mL". The lowercase letter 'l' can look like the number '1' and be confused.
- 9. The vial label lacks information regarding the manufacturer of Asclera. The manufacturer information should be included on all labels and labeling.
- 10. Revise the strength statements "5 mg/1 mL" and "10 mg/1 mL" to read as "5 mg per mL" and "10 mg per mL" or "5 mg/mL" and "10 mg/mL". The use of a slash with the number "1" is easily misinterpreted. The United States Pharmacopeia 30/National Formulary 25 (USP 30/NF 25) states that "1 mL" not be used when expressing strength per single milliliter. Strength per single milliliter should be expressed as mg/mL or mg per mL.

B. Carton Labeling

- 1. Relocate the statement ^{(b) (4)} on the back panel of the carton label to the front on the principal display panel and replace it with "Single use: Discard unused portion".
- 2. Remove the swoosh line between the proprietary name and the established name on the carton label. There should be no intervening matter that appears between the proprietary name and the established name to comply with 21 CFR 201.10(a).
- 3. Ensure the established name is at least $\frac{1}{2}$ the size and prominence of the proprietary name to comply with 21 CFR 201.10(g)(2). The proprietary name, established name, and

strength should be the most prominent information communicated on the principal display panel.

- 4. The presentation of strength on the container label, "0.5%", is difficult to read as currently printed in white font inside the gray circular-shaped graphic. Revise the white font color to another prominent color to provide adequate contrast, thereby increasing the prominence of the strength.
- 5. Add a net quantity statement such as, "contains 5 ampules each containing 10 mg/2 mL", to the principal display panel. It is important for healthcare professionals to determine the net contents of the carton in terms of the number of ampules contained inside.
- 6. Modify the word "ampoule" to read "ampule" for the correct American-English spelling.
- 7. Revise the unit "ml" for milliliter to read as "mL". The lowercase letter 'l' can look like the number 'l' and be confused.
- 8. In the NDA submission, the Applicant is stated as "Chemische Fabrik Kreussler & Co., GmbH", however the carton labeling states the Applicant as Kreussler & Co., GmbH, Germany". The manufacturer name should be identical and consistent on all labels and labeling. Revise accordingly.
- 9. Revise the strength statements "5 mg/1 mL" and "10 mg/1 mL" to read as "5 mg per mL" and "10 mg per mL" or "5 mg/mL" and "10 mg/mL". The use of a slash with the number "1" is easily misinterpreted. The United States Pharmacopeia 30/National Formulary 25 (USP 30/NF 25) states that "1 mL" not be used when expressing strength per single milliliter. Strength per single milliliter should be expressed as mg/mL or mg per mL.

Applica Type/N	tion umber	Submission Type/Number	Submitter Name	Product Name

Asclera (polidocanol) 0.5%/1%

NDA-21201

ORIG-1

CHEMISCHE FABRIK KREUSSLER & CO. GMBH

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SHIRLEY A ZEIGLER 01/07/2010

LAURA L PINCOCK 01/07/2010

DENISE P TOYER 01/07/2010

DENISE P TOYER on behalf of CAROL A HOLQUIST 01/07/2010

FOOD AND DRUG ADMINISTRATION Center for Drug Evaluation and Research Division of Drug Marketing, Advertising, and Communications

Memorandu	m
	PRE-DECISIONAL AGENCY MEMO
Date:	December 8, 2009
То:	Michael Monteleone Regulatory Health Project Manager Division of Cardiovascular and Renal Products (DCRP)
From:	Michelle Safarik, Regulatory Review Officer Division of Drug Marketing, Advertising, and Communications (DDMAC)
Subject:	Asclera (polidocanol) injection NDA 21-201 Comments on draft product labeling

DDMAC has reviewed the proposed product labeling (PI) for Asclera (polidocanol) injection (Asclera) dated July 10, 2009, and submitted for consult to DDMAC on December 4, 2009.

Thank you for your consult.

If you have any questions, please contact Michelle Safarik at 301.796.0620 or <u>michelle.safarik@fda.hhs.gov</u>.

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

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)}
			·····

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/s/

MICHELLE L SAFARIK 12/08/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		R	REQUEST FO	R CONSU	JLTATI	ON	
TO (Office/Division): DDMAC			FROM (Name, Office/Division, and Phone Number of Requestor): Michael Monteleone (DCRP) (x61952)				
date 12-4-09	IND NO.		nda no. 021201	TYPE OF DOCUMEN' NDA Resub	Γ	DATE OF D 7-10-09	OCUMENT
NAME OF DRUG PRIORITY CONSIDERATION polidocanol priority				CLASSIFICATION OF	DRUG	DESIRED C 12-11-09	OMPLETION DATE
NAME OF FIRM: Chemisc	he Fabri	k Kreussl	er & Co., GmbH				
			REASON FO	OR REQUEST			
·			I. GEN	NERAL			
NEW PROTOCOL PRE-NDA MEETING PROGRESS REPORT END-OF-PHASE 2a MEE NEW CORRESPONDENCE END-OF-PHASE 2 MEE DRUG ADVERTISING RESUBMISSION ADVERSE REACTION REPORT SAFETY / EFFICACY MANUFACTURING CHANGE / ADDITION PAPER NDA MEETING PLANNED BY CONTROL SUPPLEMEE			PRE-NDA MEETING END-OF-PHASE 2a MEE END-OF-PHASE 2 MEET RESUBMISSION SAFETY / EFFICACY PAPER NDA CONTROL SUPPLEMEN	TING RESPONSE TO DEFICIENCY LETTER TING FINAL PRINTED LABELING ING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW OTHER (SPECIFY BELOW): T			
			II. BIOM	IETRICS			
 PRIORITY P NDA REVIEW END-OF-PHASE 2 MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER (SPECIFY BELOW): 			CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER (SPECIFY BELOW):				
			III. BIOPHAR	RMACEUTICS			
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			IV. DRUG	S SAFETY	· .		
 PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP 				KETING EXPER DVERSE EXPER ALYSIS	IENCE, DRUC IENCE	USE AND SAFETY	
			V. SCIENTIFIC IN	NVESTIGATIONS			
CLINICAL				D NONCLINICAL			
COMMENTS / SPECIAL INSTRUCTIONS: Please review PI for NDA 021201 polidocanol. This is a priority resubmission with a January 10, 2010 (SUNDAY) goal date. Please return ASAP as label negotiations with the sponsor are likely to be very difficult on FDA and Sponsor side with upcoming holidays. PDF of labeling is below, word version will be sent to DDMAC PM.							
signature of requestor Michael Monteleone				METHOD OF DELIVE	RY (Check one) MAIL	MAIL	HAND
PRINTED NAME AND SIGNAT	TURE OF RE	CEIVER		PRINTED NAME AND	SIGNATURE O	F DELIVERER	
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SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 21-201
Applicant	Chemische Fabrik Kreussler and Co. GmbH
Drug Name	
	ASCLERA (polidocanol)
SUBMISSION DATE	July 10, 2009
SEALD REVIEW DATE	December 15, 2009
SEALD REVIEWER(S)	Debbie Beitzell, BSN
	This review does not identify all guidance-related labeling
	issues and all best practices for labeling. We recommend
	the review division become familiar with those
	recommendations. This review does attempt to identify all
	aspects of the draft labeling that do not meet the
	requirements of 21 CFR 201.56 and 201.57.

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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)}

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/s/

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DEBRA C BEITZELL 12/15/2009

LAURIE B BURKE 12/15/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

FOOD AND DRUG ADM							
TO (Division/Office): Mail: OSE				FROM: Michael Monteleone, Division of Cardiovascular and Renat Products			
्रताह 11-18-09	IND NO.		NDA NO. 021201	TYPE OF DOCUMENT Carton and Container labeling	DATE OF DOCUMENT 11-13-09		
NAME OF DRUG Polidocanol		PRIORITY C Priority	ONSIDERATION	CLASSIFICATION OF DRUG Sclerosant	DESIRED COMPLETION DATE 12-1-09		
NAME OF FIRM:Chemische Fabrik	Kreussler & Co	., GmbH		I			
			DEASON EO				
		-	I. GEN	IERAL			
NEW PROTOCOL PRENDA MEETING PROGRESS REPORT END OF PHASE II MEETING NEW CORRESPONDENCE RESUBMISSION DRUG ADVERTISING SAFETY/EFFICACY ADVERSE REACTION REPORT PAPER NDA MANUFACTURING CHANGE/ADDITION CONTROL SUPPLEMENT MEETING PLANNED BY HEAD			PRENDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMENT	 RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW OTHER (SPECIFY BELOW): 			
·			II. BIOM	ETRICS			
STATISTICAL EVALUATION BRAN	СН			STATISTICAL APPLICATION BRANCH			
TYPE A OR B NDA REVIEW C END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW C OTHER (SPECIEX BELOWA)				CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER (SPECIFY BELOW):			
			III. BIOPHAR	MACEUTICS			
ISSOLUTION				DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST			
IV. DRUG EXPERIENCE							
PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP				REVIEW OF MARKETING EXPERIENC SUMMARY OF ADVERSE EXPERIENC POISON RISK ANALYSIS	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS		
			V. SCIENTIFIC IN	IVESTIGATIONS			
					· · · · · · · · · · · · · · · · · · ·		
COMMENTS/SPECIAL INSTRUCTIONS:							
DMEPA – Please review carton and	l container Ial	beling in this s	ubmission. Volume will be s	ent to OSE PM, Nina Ton. Also attached b	elow.		
SIGNATURE OF REQUESTER ME Michael Monteleone				METHOD OF DELIVERY (Check one) MAIL	HAND		
ATURE OF RECEIVER				SIGNATURE OF DELIVERER			
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Application Type/Number

Submission Type/Number

Submitter Name

Product Name

NDA-21201

-----ORIG-1

CHEMISCHE FABRIK KREUSSLER AND CO GMBH AETHOXYSKLEROL (POLIDOCANOL)0.5%/19^{(b) (4)}

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/s/

MICHAEL V MONTELEONE 11/18/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Date:	October 22, 2004	Food and Drug Administration Rockville, MD 20857
То:	Jonathan K. Wilkin, M.D., Director Division of Dermatologic and Dental Drug Products (DDDDP), HFD-540 Office of Drug Evaluation V	
Through:	Mark Avigan, M.D., C.M., Director Division of Drug Risk Evaluation, HFD-430 Office of Drug Safety	
From:	Marilyn R. Pitts, Pharm.D. Postmarketing Safety Evaluator Office of Drug Safety (ODS) Division of Drug Risk Evaluation, HFD-430	
Subject:	ODS Postmarketing Safety Review – PID # 040320 Adverse Event: All Events	
Drug(s):	Sclerosing Agents – Aethoxysklerol (NDA 21-201), Sodium Tetradecyl Sulfa NDA 05-970), Sodium Morrhuate, Sodium Chloride 23.4%	te (Sotradecol®

EXECUTIVE SUMMARY

At the request of DDDDP we summarized post-marketing adverse event reports associated with the sclerosing agents aethoxysklerol, sodium tetradecyl sulfate (STS), sodium morrhuate and sodium chloride 23.4%. The information related to sodium tetradecyl sulfate is an update to the ODS Safety Review of March 11, 2002 authored by Dr. Renan A. Bonnel.¹ We provided AERS² data for all of the products, and WHO³ data for aethoxysklerol since aethoxysklerol is currently unapproved in the US.

We found 104 foreign reports for aethoxysklerol, three domestic reports for sodium morrhuate, and three new domestic reports for STS since the March 2002 analysis. There were no adverse event reports for sodium chloride 23.4% when used for dermatological indications. The patients receiving aethoxysklerol were mostly female; and were all female in the updated STS cases, as well as in the sodium morrhuate cases. The patients reported receiving the sclerosing agents primarily to treat varicose veins. Allergy/hypersensitivity and skin reactions accounted for the largest proportion of all adverse events submitted for all three products. Death associated with dermatological indications was reported in at least one and possibly 3 of the 5 aethoxysklerol cases; 6 STS cases⁴; and one sodium morrhuate case. The cause of death in these cases was primarily anaphylaxis, although one death related to aethoxysklerol reported cardiac events.

¹ Bonnel RA. ODS Safety Review – Post-Marketing Safety Review: Sodium Tetradecyl Sulfate (NDA 05-970), March 11, 2002

² Adverse Event Reporting System

 $^{^{3}}$ WHO = World Health Organization

The occurrences of anaphylaxis, hypersensitivy reactions, and localized skin reactions with sodium morrhuate are not unexpected, since the events are well described in the product label, as well as the medical literature. Adverse event reports concerning aethoxysklerol, a foreign product also listed hypersensitivity, anaphylaxis and localized skin reactions which are described in the medical literature. Although the three new STS cases reported serious outcomes associated with anaphylaxis and local skin burns, they do not represent new safety concerns since the reactions are consistent with labeling and the previous analysis. Of the six known deaths associated with the dermatological use of STS, one occurred in a patient with a history of asthma, a labeled contraindication, and one occurred after receiving the label recommended STS test dose. To be consistent with the innovator's label, the STS ANDA label currently under review should return asthma to the *Contraindication* section of the label, as well as provide information concerning the risk of thrombosis. The ANDA sponsor is recommended to submit safety information to justify omitting this important information from the proposed labeling. Additionally, the product label should continue to emphasize the necessity of being able to rapidly respond to an emergency.

Since there were four additional death reports associated with the off label use of STS to treat esophageal varices we will forward a copy of this analysis to the Gastroenterology division.

BACKGROUND

DDDDP requested that ODS provide post-marketing safety data for aethoxysklerol (NDA 21-201), a sclerosing agent that was under review to treat varicose veins of the lower extremities, as well as post-marketing safety information for sodium tetradecyl sulfate, sodium morrhuate and sodium chloride 23.4%, other sclerosing agents used in the treatment of varicose veins. Since making their initial request for information, and completion of this analysis, DDDDP has issued a non-approval (NA) letter for aethoxysklerol. According to the NA letter placed in DFS on August 2, 2004, the action was taken based on inadequate information submitted in the NDA. The reader is referred to DFS to review the NA letter if additional details are desired. Subsequently, a post-NA meeting as requested by the sponsor has been granted and is scheduled for October 13, 2004.

Sodium tetradecyl sulfate (hereafter STS), one of the sclerosing agents for which DDDDP requested additional postmarketing information was approved in 1946 for the treatment of small uncomplicated varicose veins of the lower extremities. In April 2001 marketing was suspended by the manufacturer reportedly because they ^{(b) (4)} On March 11, 2002, in response to a Citizen's Petition, the Office of Drug Safety performed a post-marketing review of STS to determine if there were unstated safety concerns which might have contributed to market suspension of the product. Just recently, on August 31, 2004 DDDDP made ODS aware of an ANDA application to re-introduce STS back to the market. ^{(b) (4)}

⁴ The AERS database describes four deaths associated with the dermatological use of STS, and the product label describes four deaths, however, it appears that only two of the deaths are common in both series. Therefore, we include six deaths associated with STS use when treating dermatological conditions.

Consequently, DDDDP has requested additional detailed AERS information concerning STS associated death, and thrombosis adverse event reports.

Please note that the medical literature provide multiple citations describing the use of STS, sodium morrhuate, hypertonic saline and aethoxysklerol in treating serious, and potentially life-threatening esophageal varices. However, discussion of adverse events reports related to gastrointestinal uses of the sclerosing agents is beyond the scope of this analysis, consequently we will send a copy of this analysis to the Gastrointestinal Division as an item of information.

This document is organized into four parts:

- Part I: Aethoxysklerol a review of adverse event reports from the AERS and WHO databases.
- Part II: Sodium Tetradecyl Sulfate a review of new adverse event reports received since the March 11, 2002 review.
- Part III: Sodium Morrhuate a review of adverse event reports associated with dermatological indications.
- Part IV: Sodium Chloride 23.4% a review of adverse events reports associated with dermatological indications.

LITERATURE

A MEDLINE search of the English-language literature published from 1966 to 2004 found case reports^{5,6} describing aethoxysklerol associated allergic and anaphylactic reactions, and sodium morrhuate⁷ associated fatal anaphylaxis. We did not find new case reports published since March 11, 2002 concerning STS, and we did not find any case reports of adverse events associated with concentrated sodium chloride when used as a sclerosing agent.

PRODUCT INFORMATION AND LABELING

Aethoxysklerol

The product label for the foreign aethoxysklerol product was unavailable for review.

Sodium Tetradecyl Sulfate (Sotradecol®)⁸

The adverse events listed below are found in the following sections of the Sotradecol® (STS) product label:

⁵ Feied CF, Jackson JJ, Bren TS et al. Allergic reactions to polidocanol for vein sclerosis. Two case reports. J Dermatol Surg Oncol. 1994 Jul;20(7):466-8.

⁶ Stricker BH, van Oijen JA, Kroon C, et al. Anaphylaxis following use of polidocanol. Ned Tijdschr Geneeskd. 1990 Feb 3;134(5):240-2. In german, however, abstract is in english.

⁷ Jackson CB. Anaphylactoid reaction with death following the injection treatment of varicose veins with sodium morthuate. J Med Assoc Ga. 1955 Jan;44(1):25.

Warnings

... severe adverse local effects, including tissue necrosis may occur following extravasation ... Allergic reactions, including anaphylaxis have been reported that led to death.

... as a precaution against anaphylactic shock, it is recommended that 0.5ml of STS be injected into a varicosity, followed by observation of the patient for several hours before administration of a second or larger dose. The possibility of an anaphylactic reaction should be kept in mind, and the physician should be prepared to treat appropriately.

Precautions

... danger of thrombosis extension into the deep venous system ... Embolism may occur as long as four weeks after injection of sodium tetradecyl sulfate.

Adverse Reactions

Local reactions consisting of pain, urticaria or ulceration may occur at the site of injection. Sloughing and necrosis of tissue may occur following extravasation.

Allergic reactions such as hives, asthma, hayfever and anaphylactic shock have been reported. Mild systemic reactions ... including headache, nausea and vomiting.

Four deaths have been reported with the use of Sotradecol[®]. Two cases reported anaphylactic shock leading to death, one case reported a fatal pulmonary embolism in a 36-year-old female who was not taking oral contraceptives, and the fourth case was in a patient who concomitantly used an anti-ovulatory agent.

Contraindications

STS is contraindicated in patients with a previous hypersensitivity reaction to the product, as well as in patients with a number of uncontrolled systemic conditions, including, but not limited to asthma and diabetes mellitus.

Sodium Morrhuate⁹

The following information is found in the *Precautions* section of the sodium morrhuate label:

Localized burning or cramping, urticaria, sloughing and necrosis if extravasation occurs, drowsiness, headache, pulmonary embolism, hypersensitivity characterized by dizziness, weakness, vascular collapse,

⁸ PDR 1999. Sotradecol® Product label. Page 971.

⁹ PDR 1999. Scleromate® Product label. Page 1285.

asthma, respiratory depression, gastrointestinal disturbance (i.e., nausea, vomiting) and urticaria. Anaphylaxis may also occur.

Morrhuate sodium should only be administered when adequate facilities, drugs (i.e., epinephrine, antihistamines, corticosteroids), and personnel are available for the treatment of anaphylactic reactions.

Additionally, the *Dosage* section states "To determine the possibility of sensitivity to the drug, some clinicians recommend injections of 0.25 to 1ml of 5% morrhuate sodium into a varicosity 24 hours before administration of a large dose."¹⁰

CASE SELECTION

We conducted separate searches of the AERS database for all adverse event reports associated with the sclerosing agents sodium tetradecyl sulfate (STS), sodium morrhuate, aethoxysklerol (polidocanol), and sodium chloride 23.4%. Additionally, since aethoxysklerol is not marketed in the US, we searched the World Health Organization's Adverse Reactions Database (Vigisearch). The results and the dates of the individual searches are reviewed in separate sections. We exported demographic data for all reports to an interactive database for analysis. As such, the data for reports with an outcome other than death may contain duplicate reports. We were unable to conduct an indepth hands-on analysis of the death reports obtained from the WHO database, since the original source documents were unavailable.

Part I: Aethoxysklerol (Polidocanol)

On May 18 and 20, 2004 we respectively searched the AERS and WHO Vigisearch (hereafter WHO) databases for all adverse event reports associated with the use of aethoxysklerol (polidocanol). We searched the WHO database under the preferred base name¹¹ of polidocanol.

Overview of all aethoxysklerol reports

We found 104 worldwide adverse event reports listing aethoxysklerol as a suspect agent (AERS 1, WHO 103). There were 95 females, 21 males and eight cases of unreported gender. The patients ranged in age from 14 years to 77 years, with a median age of 47 years old (n=85). All reports, from all sources were of foreign origin. We were unable to determine if the single AERS case is a duplicate to a case retrieved from the WHO database.

The WHO database reported six cases of death (representing 5 unduplicated cases), 59 cases of recovery, 11 cases that did not recover, and 27 cases where the outcome was unknown. The single case retrieved from the AERS database reported hospitalization. Due to the limitations of the data retrieved from the WHO database, we were only able to perform a limited

¹⁰

¹¹ The preferred base name provides the broadest search, capturing the preferred base, salts for the same generic, and all corresponding trade names. The results are returned as line listings, or as a case report, without a narrative.

review of the death cases. Additionally, we did not perform a review of the non-death cases, and therefore do not know how many cases described hospitalization, or life-threatening outcomes.

Top Twenty Adverse Event Terms Reported:

A listing of the 20 most commonly reported adverse event terms associated with aethoxysklerol is provided in the table below. Of note, a report may contain unlimited adverse event terms. The most prevalent adverse event terms reported were related to allergy or hypersensitivity reactions (42), followed by central nervous system reactions (27), local skin reactions (13), and gastrointestinal reactions (12). Since we did not have access to the aethoxysklerol label, it is unknown at this time how many of the reported adverse event terms are found in the foreign product's label.

Adverse Event ¹²	Case Count
Rash Erythematous	12
Urticaria	8
Dyspnoea	8
Headache	7
Dizziness	7
Injection Site Reaction	7
Hypotension	6
Skin Necrosis	6
Allergic Reaction	5
Pruritis	5
Malaise	5
Anaphylactic Shock	4
Vision abnormal	4
Taste perversion	4
Stomatitis	4
Nausea	4
Intermenstrual Bleeding	4
Hypoaesthesia	4
Fever	4

Table 2 – Twenty Most Frequent Adverse Event Terms reported for Aethoxysklerol

Death (WHO - 6 reports representing 5 unique cases)

¹² Of note, a report may contain unlimited adverse event terms.

There were six WHO reports¹³, representing five unique cases (male -3, female -2) describing outcomes associated with death. The WHO outcome description for death included "died" (1), "died – reaction may be contributory" (3, 1 duplicate), and "died – unrelated to reaction" (1).

The patients who died ranged in age from 54 to 69 years, with a median age of 54 years (n = 5). Aethoxysklerol was used in this subset of patients to treat varicose veins (1), varicose veins of the esophagus (1), and esophageal varices (1). Two cases did not report the indication for use of aethoxysklerol. Reported adverse events included anaphylaxis (2), cardiac failure (1), and hepatic + acute renal + respiratory failure (1). In three patients the WHO database classified anaphylaxis and cardiac failure as being contributory to the outcome of death. A fourth death case was not assigned a causality category, and the fifth death case was classified as unrelated to the reaction. The fifth case reported multiple systemic events including hypotension, pulmonary hypertension, arrhythmia, bradycardia and respiratory insufficiency. Two of the five death cases reported using concomitant medications that may have contributed to the adverse event. The concomitant medications were cimetidine, listed as a co-suspect agent in the case reported the amount of aethoxysklerol used; three cases reported receiving an unreported concentration of aethoxysklerol in doses of 12ml, 37ml and 45ml, and a fourth case reported receiving 20mg. The fifth case did not report the amount of aethoxysklerol used.

Hospitalization (AERS - 1)

The AERS¹⁴ case was of a 73-year old male who received carbocaine 1% (10ml) and aethoxysklerol (90ml) to treat varicose veins in each leg. The patient experienced a localized skin reaction progressing to necrosis ten days after treatment, was hospitalized, and subsequently underwent a split-skin graph. No further information was provided.

Part II: Sodium Tetradecyl Sulfate

Overview of all Sodium Tetradecyl Sulfate Reports

This section is an update to the March 11, 2002 STS Post-Marketing Safety Review conducted by Dr. Renan A. Bonnel of the Office of Drug Safety.¹⁵

Dr. Bonnel found 171 unduplicated AERS cases of adverse events associated with the use of STS, of which 154 were analyzed¹⁶. The analysis included 146 US and eight foreign cases. The cases reported outcomes including death (4), hospitalization (34), life-threatening (1), and disability (1). The remaining outcomes were non-serious. STS was given to treat superficial varicose veins (77%), esophageal varices (13%), and non-FDA approved indications (10%) including epitaxis, hemorrhoids, and hemangiomas. Overall, skin and anaphylactic/immune

¹³ WHO Reference numbers: 0784551, 0788433 + 0842208, 0842288, 1386217, 0840802

¹⁴ AERS ISR # 3104071-4, Foreign, 1998

¹⁵ Bonnel RA. ODS Safety Review – Post-Marketing Safety Review: Sodium Tetradecyl Sulfate (NDA 20-087), March 11, 2002

¹⁶ Seventeen cases were excluded for reasons including the primary suspect agent was a drug other than sodium tetradecyl sulfate; illegibility of some reports; unevaluable reactions; and data was submitted from randomized clinical trials involving several agents where the adverse events were not separated out for individual agents.

reactions accounted for the largest proportion of all adverse events submitted for STS. Attributions of STS in skin and/or anaphylactic/immune cases were supported by good temporal relationships, well-documented clinical presentations, and in some cases positive dechallenge responses. Other adverse events reported included serious gastrointestinal¹⁷ events associated with the unapproved use of STS, as well as a small number of cases reporting orbital hemorrhages following craniofacial sclerotherapy. However, the causal role of STS in the latter cases was less certain due to confounding factors, including the risk of the surgical procedures themselves.

Death (4)

There were eight STS-related cases with a coded outcome of death, of which all were reported at the time of the March 11, 2002 review. Four of the eight reports were excluded from final review. Two of the excluded cases described STS associated fatal bacterial peritonitis in complicated patients with histories of alcohol abuse who received STS for esophageal varices.¹⁸ A third excluded case was a summary article of a clinical trial mentioning the deaths of two patients who had inoperable hepatic cancer¹⁹; and the fourth excluded case (foreign) was a patient with a history of diabetes mellitus, a contraindication to the use of STS. This case report was intermittently illegible, but described sepsis, shock, pleural effusion, pyrexia and death. The patient had received STS to treat varices. Brief narratives of these cases are provided in the appendix.

We included four cases in our analysis of STS associated death in patients treated for dermatological indications. All cases reported death occurring after anaphylaxis. All of these cases were of US origin, and included two females, and two cases with unreported gender. Two cases reported the ages of the patients (36 years and 60 years), and two cases did not. The patients received STS for varicose veins (1) and "hairline veins" (1). The indication for use in the other two cases was unreported, although it appears that administration of STS occurred in the office setting, which strongly supports the patients being treated for dermatological indications. Anaphylaxis (or symptoms) developed very soon after administration of STS in all four patients, with one patient reporting anaphylaxis occurring after the administration of the recommended test dose. The other three cases provided insufficient information concerning test dosing. One patient had a history of asthma, a contraindication to STS use. Other relevant history, if present was unreported in the remaining three patients. Brief narratives of these cases are provided in the appendix.

Embolism (1)

We found one case of pulmonary embolism possibly related to STS administration. This case was analyzed in the March 11, 2002 review, and is of a 52-year old female who received multiple doses of STS to treat varicose veins. Approximately one week after her first series of doses the patient developed shortness of breath. The patient was admitted to the hospital, with a diagnosis of "embolism". The patient was treated with heparin and subsequently

¹⁷ Peritonitis, hemorrhage

¹⁸ Schembre D, Bjorkman DJ. Post-Sclerotherapy Bacterial Peritonitis. Am J Gastroenterology 1991;86:481-486.

¹⁹ Sung JJ, Yeo W, Suen R, et al. Injection sclerotherapy for variceal bleeding in patients with hepatocellular carcinoma: cyanoacrylate versus sodium tetradecyl sulphates. Gastrointest Endosc 1998;47:235-239.

recovered. The patient reportedly was a "heavy" smoker and was concomitantly using conjugated estrogens. No further information was provided.

New Cases since March 11, 2002 Review

We searched the AERS database on August 4, 2004 and found three new cases of adverse events associated with STS since the March 11, 2002 review. All three cases were of US origin, were female and had received STS to treat varicose veins of the lower extremities. The patients were aged 45, 46 and 50 years old. Reported adverse events included a swollen tongue (1), chest pain + hives (1), and full thickness burns on both ankles (1). The events occurred after one dose in two patients, and after two doses in the third. There were no new reports of deaths in these three new cases, although, two patients were hospitalized, and one patient received treatment through multiple visits to a burn center. STS is labeled for hypersensitivy and severe local reactions, and therefore the role of STS in the development of the swollen tongue, hives and localized skin reactions (burns) is strongly supported.

Part III: Sodium Morrhuate

Overview of all Sodium Morrhuate Reports

On May 14, 2004 we searched the AERS database for all adverse event reports associated with sodium morrhuate. We found eight reports, of which we excluded five reports where sodium morrhuate was not used for dermatological indications²⁰. We reviewed three reports where the patients were administered sodium morrhuate to treat varicose veins (2), and multiple spider veins + varicose veins (1). All three reports were of US origin, and all patients were female. The women were aged 43 (2), and 39 years (1). Two patients were hospitalized and one patient had a non-serious outcome.

The adverse events in the two hospitalized cases included one patient developing a hypersensitivity reaction manifested as generalized urticaria, flushing and swelling of the lips and left ear. This patient had received without incident two prior treatments with sodium morrhuate approximately three months earlier. The second hospitalized case reported systemic adverse events occurring within 24 hours of multiple injections of sodium morrhuate into leg varicose veins. Adverse events included increases in blood amylase, lipase and blood pressure, as well as dizziness, hematuria, ketonuria, lethargy, nausea, pain and proteinuria. The patient was admitted to the hospital and released after two days. The patient did not report concomitant medication use, and reported no relevant medical history. The third patient was not hospitalized, but developed systemic adverse events one to two days after receiving one dose of sodium morrhuate for multiple spider veins and varicose veins. The patient developed weakness, sweating, nausea, abdominal pain, hematuria, diarrhea, arthralgia and burning on urination. The patient was treated for a urinary tract infection with no improvement. The adverse events of urticaria, dizziness, nausea, weakness, abdominal symptoms and hypersensitivity reactions are found in the product label.

Part IV: Sodium Chloride 23.4%

²⁰ Non-dermatological indications included hemorrhoids, esophageal bleeding, gastric varices, variceal bleeding

Overview of all Sodium Chloride 23.4% Reports

On May 17, 2004 we searched the AERS database for all adverse event reports associated with sodium chloride 23.4%. We found three reports. We excluded all three reports since none of the reports used sodium chloride for dermatological indications. Two reports used sodium chloride as an ingredient in parenteral solutions, and one report was of a potential medication error due to the packaging of sodium chloride 23.4% being very similar to another product.

Discussion and Conclusion

DDDDP requested adverse event information concerning the sclerosing agents aethoxylsklerol, STS, sodium morrhuate and sodium chloride 23.4%. ODS was also asked to provide recommendations for the STS label of an ANDA application currently being reviewed by DDDDP and the Office of Generic Drugs, because important information was omitted from the ANDA applicant's product label.²¹ In response ODS reviewed all adverse event reports associated with the dermatological use of aethoxylsklerol, STS and sodium morrhuate. We did not review reports for sodium chloride 23.4% since reports found were for non-dermatological indications. Additionally, the information for aethoxysklerol contains cases where the product was used for both dermatological and nondermatological reasons.

We found adverse event reports in the AERS and/or WHO databases, and the medical literature associated with all of the agents, except sodium chloride 23.4%. In our AERS case series, the agents were used primarily for dermatological indications.²² The majority of reports were domestic, except for aethoxysklerol, which is unapproved in the US. Death associated with dermatological indications was reported in at least one and possibly three of the five aethoxysklerol cases; six STS cases; and one sodium morrhuate case. The death case associated with sodium morrhuate was reported in the medical literature, and was not found in the AERS database. Four of the six STS death cases described anaphylaxis, with one of the four receiving a test dose prior to the onset of fatal anaphylaxis. Additionally, the fatal pulmonary embolism case described in the STS label was not the same AERS case reporting hospitalization. The product labeling for STS and sodium morthuate both describe anaphylaxis, and in the case of STS, anaphylaxis associated with death. Both STS and sodium morrhuate's product label provide information on using a test dose as a precaution against anaphylaxis, and the need to provide emergency medical care when necessary.

The occurrences of anaphylaxis, hypersensitivy reactions, and localized skin reactions with sodium morrhuate are not unexpected, since the events are well described in the product label, as well as the medical literature. Aethoxysklerol, a foreign product also reported hypersensitivity, anaphylaxis and localized skin reactions which are described in the medical literature. Although the three new STS cases reported serious outcomes associated with anaphylaxis and local skin burns,

²¹ The submitted ANDA application lacked specific information concerning the risk of deep venous thrombosis, as well as lacked contraindication information in patients with a history of asthma. ²² Varicose veins, spider veins

they do not represent new safety concerns since the reactions are consistent with labeling and the previous analysis.²³ Of the six known deaths associated with the dermatological use of STS, one occurred in a patient with a history of asthma, a labeled contraindication, and one occurred after receiving the label recommended STS test dose. To be consistent with the innovator's label, the STS ANDA label currently under review should return asthma to the *Contraindication* section of the label, as well as provide information concerning the risk of thrombosis. Additionally, the product label should continue to emphasize the necessity of being able to rapidly respond to an emergency.

Since there were four additional death reports associated with the off label use of STS to treat esophageal varices we will forward a copy of this analysis to the Gastroenterology division.

Marilyn R. Pitts, Pharm.D Acting Team Leader, Safety Evaluator

cc:

NDA: 05-970 NDA: 21-201

Electronic only cc:

HFD-400/Seligman HFD-430/Avigan/Karwoski/Nguyen/Mackey/Sodium Tetradecyl Sulfate/Sodium Morrhuate/Aethoxylsklerol HFD-540/Carr/Vaughn/Luke/Bhatt/Cross/Kozma-Fornaro HFD-180/Korvich/Dubeau/Strongin

²³ Bonnel RA. ODS Safety Review – Post-Marketing Safety Review: Sodium Tetradecyl Sulfate (NDA 20-087), March 11, 2002

Appendix I – Sodium Tetradecyl associated Death Cases

Death Cases Associated with Dermatological Indications (4)

FDA 4696985, MFR# 111789, 1989, US. – **Anaphylactic reaction.** A 60-year-old female received STS to treat varicose veins. The patient lost consciousness after receiving a test dose of 0.5% STS. The patient experienced seizures. The medical team was unable to establish an airway. The patient expired three days after the test dose and ensuing adverse events. An autopsy diagnosed severe cerebral edema associated with cerebral anoxia secondary to complications of apparent anaphylactic reaction. The patient's history is significant for other allergies, having experienced a paroxysmal reaction to diazepam injection during a gastroscopy.

Reviewer's Comment: Anaphylaxis resulting in death is a labeled adverse event for STS. This patient died after receiving the test dose of the product. This may be one of two death cases from anaphylactic reaction described in the product label.

FDA 4696985, Direct, 1990. US. – Anaphylactic reaction. A physician reported that a clinic patient collapsed, developed anaphylactic shock and died after receiving STS for sclerosis. The treating physician (not the reporter) was out of town when the patient died. No further information was provided.

Reviewer's Comment: Anaphylaxis resulting in death is a labeled adverse event for STS. This may be one of two death cases from anaphylactic reaction described in the product label.

FDA 5292108, MFR # 8-95216-007L, 1995, US. – Anaphylactic reaction. A physician reported that another

physician's patient died from "fatal anaphylaxis" coincident with STS administration. No further information was provided.

Reviewer's Comment: Anaphylaxis resulting in death is a labeled adverse event for STS. This may be one of two death cases from anaphylactic reaction described in the product label.

FDA 4436602, Direct, 1985, US. – Anaphylactic reaction. A 36-year-old female received a series of STS

injections to treat "hairline veins". The patient developed "anaphylactic shock" and died at the doctor's office. The

patient had a history of allergic conditions, including eczema and asthma. No further information was provided.

The death appeared to have occurred in 1973, although the report was dated 1985.

Reviewer's Comment: Anaphylaxis resulting in death is a labeled adverse event for STS. This may be one of two death cases from anaphylactic reaction described in the product label.

Death Cases Described in the Product Label (2)

Product Label – Fatal Pulmonary Embolism. A 36-year old female experienced a fatal pulmonary embolism.

The patient was not taking concomitant oral contraceptives.

Reviewer's Comment: This case is not found in the AERS database, but is listed in the product label in the Adverse Event Section. It is unknown to this reviewer when this information was added to the label.

Product Label – Death, NOS. A patient died. The patient was concomitantly taking an "anti-ovulatory" agent.

Reviewer's Comment: This case is not found in the AERS database, but is listed in the product label in the Adverse Event Section. It is unknown to this reviewer when this information was added to the label.

Excluded Death Cases Associated (4 reports, describing 5 deaths)

FDA 4504327, MCN 080386, 1986, Foreign. – **Unknown. Report Partially Illegible.** A patient of unknown age and gender with a history of insulin dependent diabetes and liver cirrhosis received STS via endoscopy to treat esophageal varices. The patient died an unknown time after receiving STS. The patient had developed sepsis, shock, pleural effusion and pyrexia. The report was illegible in many sections.

Reviewer's Comment: This is a report of a death following STS use for an unlabeled indication and lacked sufficient detail.

FDA 4929240, MCN 892316006F, Literature Report: Schembre D, Bjorkman DJ. Am Journal of

Gastroenterology, **1991**; **86:481-486. US.** This was case 6 of the article. A 43 year old alcoholic male was admitted to the hospital for melena and increasing ascites. The patient developed hematemesis and underwent sclerotherapy with STS (12ml) on days three and six. The patient's condition continued to worsen, and underwent paracentesis for increasing girth. Ascitic cultures grew *citrobacter freudii* and antibiotics were restarted. The patient died on day nine. Autopsy showed 4+ liters of ascitic fluid and two small ulcers in the distal esophagus, without perforation. Blood, ascetic and lung cultures grew *Pseudomonas aeruginosa*.

Reviewer's Comment: This case is from an article describing bacterial peritonitis after the use of endoscopic variceal sclerotherapy. This was a retrospective review of 213 procedures among 65 patients over a 3 year period. There were six cases that developed bacterial peritonitis after the use of STS. Two of the six cases reported death.

FDA 4929241, MCN 892316004F, Literature Report: Schembre D, Bjorkman DJ. Am Journal of

Gastroenterology 1991; 86:481-486. US. This was case 4 of the article. A 58 year old alcoholic male with a long history of alcohol abuse and multiple alcohol-related medical problems was admitted to the hospital with active hematemesis and a SBP of 60 mmHg. The patient had a distended, non-tender abdomen. Several large varices were sclerosed with 11.5ml of STS which controlled the bleeding. On day two, after sclerotherapy the patient developed increasing abdominal pain, distention with decreased bowel sounds and a temperature of 38.9°C. The patient followed a rapid downhill course and died 4 days later. Autopsy showed ascites, right pleural effusion, and all cavities grew *E. coli*.

Reviewer's Comment: This case is from an article describing bacterial peritonitis after the use of endoscopic variceal sclerotherapy. This was a retrospective review of 213 procedures among 65 patients over a 3 year period. There were six cases that developed bacterial peritonitis after the use of STS. Two of the six cases reported death.

FDA 3130902, MCN 898177074A, Literature Report: Sung JJ, Yeo W, Suen R, et al. Gastrointestinal Endoscopy 1998;47:235-239. Foreign. This report describes two deaths that occurred after receiving STS during the index administration of STS to treat variceal bleeding associated with hepatocellular carcinoma. The individual cases were not reviewed.

Reviewer's Comment: This article describes treating patients with hepatocellular carcinoma complicated by variceal bleeding. Two patients in each treatment group died due to hepatic failure and uncontrolled bleeding.

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

/s/ Marilyn Pitts 10/22/04 04:57:11 PM DRUG SAFETY OFFICE REVIEWER

Mark Avigan 10/25/04 11:44:20 AM DRUG SAFETY OFFICE REVIEWER

Public Health Service

Division of Scientific Investigations Office of Medical Policy Center for Drug Evaluation and Research Food and Drug Administration Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE:	July 13, 2004
TO:	Frank Cross, Senior Regulatory Health Project manager Division of Dermatologic and Dental Drug Products, HFD-540
THROUGH:	Khin Maung U, M.D., Branch Chief, Good Clinical Practice Branch I (HFD-46), Division of Scientific Investigations
FROM:	Roy Blay, Ph.D., Good Clinical Practice Branch I, HFD-46
SUBJECT:	Evaluation of Clinical Inspections
NDA:	NDA 21-201
PROTOCOL:	Double Blind Prospective Randomized Comparative Multicenter Trial between Aethoxysklerol (polidocanol) and Sotredecol (sodium tetradecyl sulfate) in the Management of Varicose Veins of the Lower Extremities
SPONSOR:	Chemische Fabrik Kreussler
DRUG:	Aethoxysklerol (polidocanol)
INDICATION:	Treatment of varicose veins of the lower extremities
CHEMICAL CLASSIFICATION:	1
THERAPEUTIC CLASSIFICATION:	S
INSPECTION SUMMARY GOAL DATE:	June 11, 2004
ACTION GOAL DATE:	August 4, 2004

I. BACKGROUND

On March 11, 2004, inspection assignments were issued to the district offices to inspect three domestic sites, where Drs. Lohr, Pfeifer, and Goldman were principle investigators for this protocol. The purpose of the inspections was to validate data in support of pending NDA 21-201 for treatment of varicosities of the lower extremities.

The objective of the study was to evaluate the safety and efficacy of Aethoxysklerol compared to Sotradecol, an FDA-approved sclerosing agent, in subjects with varicose veins of the lower extremities. The primary efficacy parameter was the disappearance of varicosities as judged by three independent vascular surgeons comparing baseline photographs with photographs taken 16 weeks after treatment. Subjects 18-65 years of age with varicose veins of the lower extremities that met the specific inclusion criteria were treated in the following manner: veins under 1 mm received either 0.50% Aethoxysklerol or 0.25% Sotradecol; veins between 1 and 3 mm received 1.0% Aethoxysklerol or 0.5% Sotradecol; and veins between 3 and 6 mm received 3.0% Aethoxysklerol or 1.5% Sotradecol

The clinical sites of Drs. Lohr, Pfeifer, and Goldman submitted data that were essential to the approval of this submission; thus, they were selected for inspection. The goals of inspection included validation of submitted data and compliance of study activities with applicable statutes and Federal regulations. Among the study elements

reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, documentation of serious adverse events, and accuracy of drug disposition records.

II. RESULTS (by site)

NAME	CITY	STATE	ASSIGNED DATE	EIR RECEIVED DATE	CLASSIFICATION/FILE
					NUMBER
Joann Lohr	Cincinnati	OH	11 Mar 2004	Pending*	Pending/NAI*
John Pfeifer	Troy	MI	11 Mar 2004	Pending*	Pending/OAI*
Mitchel Goldman	La Jolla	CA	11 Mar 2004	7 Jun 2004	011209/OAI*

*Note that all classifications are tentative pending receipt and/or review of EIRs for each of these sites.

Site #1 Joann Lohr, M.D.

6350 Glenway Avenue, Suite 208, Cincinnati, OH 45239

In this "Ohio study," 150 subjects were enrolled with data collected on 142 subjects.

Per recent telephone discussion with Tom Nojek, FDA inspector, Cincinnati District, a Form 483 was not issued to Dr. Lohr as the FDA inspection revealed no significant deficiencies. Based on this verbal communication, this inspection is classified NAI.

Comment: At this point in time, it appears that data from subjects at this site can be used in support of the primary efficacy endpoint analysis in NDA 21-201.

Site #2 John Pfeifer, M.D. Institute for Vein Disease 3290 West Big Beaver, Suite 410, Troy, MI 48084

41 subjects were enrolled with data collected on 38 subjects.

Dr. Pfeifer was issued a six-page typed Form 483 with more than 50 observations. These inspectional observations included the following:

- 1. Not conducting the study in accordance with the investigational plan:
 - a. Seven subjects did not receive the proper concentration of the comparator drug, Sotradecol.
 - b. The unblinded investigator serving as the vascular technician was not listed on the Form 1572.
 - c. One subject was unblinded to the study.
 - d. One subject included in the study should have been excluded because of morbid obesity, as specified in the protocol.
 - e. Nine subjects enrolled into the study should have been excluded because of venous reflux/valvular incompetence, as specified by the protocol.
 - f. For seven subjects, the areas of treatment were not photographed at baseline and/or at scheduled post-treatment dates, as specified by the protocol.
 - g. Five subjects were excluded from the study as a result of receiving undiluted Sotradecol (this observation may be reclassified as a deviation from protocol pending review of the EIR). Drug ledgers do not indicate that any of the subjects in the 3100 series (vein sizes ≤ 1 mm) or 3200 series (1mm \leq vein size ≤ 3 mm) received Sotradecol at the required 0.25% or 0.50% dilutions, respectively.

(Note: Of the protocol violations above, items a, c, d, e, f and g are considered important for the integrity of the primary efficacy endpoint. Thus, the subjects associated with these observations should not be included in the primary efficacy analysis)

- 2. Inadequate drug disposition records:
 - a. Drug Accountability Control Records lack lot numbers for the different concentrations of Aethoxysklerol

and Sotradecol that were used.

- b. Individual Drug Accountability Ledgers list the volume of drug used for each subject but not the number of ampoules. In addition, not all ampoules of the study drug or the comparator were accounted for in these records.
- c. Accountability Ledgers were revised changing the dates of treatment or the amounts of the study drugs, and the identities of five subjects, without annotating an explanation or the dates on which the changes were made.
- (Note: *Of the observations above, item c is considered important for the integrity of the primary efficacy endpoint. Thus, these five subjects should not be included in the primary efficacy analysis*)
- 3. Inadequate record keeping:
 - a. Venous photoplethysmographs (PPGs) were done on subjects throughout the study, but they were marked "Not Done" on the Case Report Forms (CRFs).
 - CRFs, accountability ledgers, and medical charts were revised without an annotated explanation or the dates on which the revisions were made. Subject identities on photos were corrected using sticky notes. Other revisions to documentation leave in question what drug was administered and in what concentration. Such revisions to documents were observed in documents/photos for seven subjects.
 - c. Medical records were missing for four subjects.
- (Note: The three observations above are considered important for the integrity of the primary efficacy endpoint. Thus, the subjects associated with these observations should not be included in the primary efficacy analysis)
- 4. Inadequate informed consent process:

Two subjects received screening tests prior to the dates of their signatures on the consent form.

- 5. <u>Inadequate reporting to the IRB</u>:
 - a. The protocol violation regarding subjects receiving the comparator drug at concentrations greater than that specified by protocol (see 1.a.) was not reported to the IRB.
 - b. Two subjects experienced adverse events (i.e., ulcerations, large ecchymosis, and a thrombosed vein) that were not reported to the IRB.
- 6. Inadequate assurance of IRB oversight:

A consent form dated August 10, 1992, was used throughout the study but was not approved by the IRB. The IRB had approved an earlier version dated June 8,1992.

- NOTE: These observations are extracted solely from the Form 483 issued to the investigator. The Establishment Inspection Report containing the full report and supportive exhibits has not been received and reviewed. Based on the Form 483 alone, there are a significant number of subjects that should be excluded from the primary efficacy analysis.
- Conclusion: At this point in time, it appears that data from several subjects at this site can NOT be used in support of the primary efficacy endpoint analysis in NDA 21-201.

Site #3 Mitchel Goldman, M.D.

7630 Fay Avenue, La Jolla, CA 92037

138 subjects were randomized and 129 subjects completed the clinical study.

Dr. Goldman was issued a six-page typed Form 483 with more than 40 observations. These observations included the following:

1. Not conducting the study in accordance with the investigational plan:

- a. Seven subjects received study drug (either Aethoxysklerol or Sotradecol) exceeding the maximum protocolspecified daily dose of 2mg/kg/day. These subjects continued in the study.
- b. The unblinded investigator participated in all pre-screening procedures as well as post-treatment follow-up evaluations; the protocol required that the unblinded investigator refrain from participation in follow-up evaluations.
- c. The blind was broken for one subject.
- d. The protocol required the PI to sign all consent forms. None of the consent forms were signed by the PI. Also, none of the on-study consent forms were signed by the PI.
- e. Flow Sheets for subjects were required by protocol to be reviewed weekly by the PI. None of the Flow Sheets for any of the 63 subjects were signed by the PI. Final Evaluation Reports required by protocol were not filled out for any of the subjects.
- f. An obese subject was not excluded from the study, as required by protocol.
- g. Microthrombectomy was to be performed with a No. 65 Beaver Blade. On four subjects, microthrombectomy was performed using various gauge needles.
- h. Three subjects were treated with Diprolene cream to minimize inflammation in the area of the injected vein. The protocol required assessment of inflammation after treatment.
- i. Photographs of at least four subjects at baseline and/or at specified post-treatment intervals were either not done or taken of non-comparable areas (e.g., one subject's baseline and one month post-treatment photos were of the ankle while the final four month post-treatment photograph was of the back of the leg).
- j. Photographic evaluations of at least three subjects were not conducted by the PI.
- (Note: Of the protocol violations above, items a,b, c, f, h, i and j are considered important for the integrity of the primary efficacy endpoint. Thus, the subjects associated with these observations should not be included in the primary efficacy analysis.)
- 2. Inadequate drug records:
 - a. Drug Distribution Records (DDR) do not indicate that three subjects who were treated received any of the study drugs.
 - b. The DDR do not document the receipt of Sotradecol, lot # 102208; however, the Drug Accountability Ledger (DAL) documents that two subjects received this lot number.
 - c. The DDR do not document receipt of Sotradecol, lot # 094202, but the Final Drug Inventory Form shows four packages of this lot number returned.
 - d. The DAL is inaccurate in that three subjects received more of the study drug than indicated on the DAL.
- (Note: *Of the observations above, items a and d are considered important for the integrity of the primary efficacy endpoint. Thus, the subjects associated with these observations should not be included in the primary efficacy analysis.*)
- 3. Inadequate supervision of the study by the PI:
 - a. Flow sheets were not reviewed and signed on a weekly basis by the PI
 - b. Final Evaluation Reports were not prepared for any subject in the study by the PI.
 - c. Source documents including follow-up evaluations were not signed or initialed by the PI on a routine basis.
 - d. Proper training of the unblinded investigator regarding proper dosing was not assured by the PI. Seven subjects were overdosed.
 - e. The PI was not routinely involved in photographic evaluations.
 - f. The PI could not identify the individual "RG" even though this person's initials are on source documents and CRFs for three subjects.
- (Note: Of the observations above, items a, d and e are considered important for the integrity of the primary efficacy endpoint. Thus, the subjects associated with these observations should not be included in the primary efficacy analysis.)
- 4. Inadequate informed consent form:

The consent form does not address the extent to which the confidentiality of the consent forms would be maintained (i.e., that such forms may be inspected by the FDA).

5. Inadequate record keeping:

Multiple records for at least four subjects are missing.

6. Lack of IRB approval:

A health education newsletter containing recruitment information for this trial was not submitted to the IRB for approval.

- 7. The PI did not indicate on his financial disclosure statement whether he did or did not have a financial interest in the study.
- NOTE: These observations are based on a brief review of the Form 483 and accompanying EIR. Based on this brief review alone, there are a significant number of subjects that should be excluded from the primary efficacy analysis.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data submitted in support of this application by Dr. Lohr (the "Ohio Study") appear adequate based upon our verbal discussion with the FDA inspector (a Form 483 was not issued); at this time no documentation regarding the inspection has yet been received for review.

For the data from the sites of Drs. Pfeifer and Goldman (the "MICA Study"), there is <u>insufficient</u> documentation to assure that all subjects fulfilled the eligibility criteria or that the enrolled subjects received the assigned study medication in the dose specified by the protocol or that the primary clinical efficacy endpoints (and photographic records pre- and post-treatment) were appropriately recorded and verifiable or that all enrolled subjects were available for the duration of the study and completed the clinical trial. Thus, the data submitted in support of this application by Drs. Pfeifer and Goldman are inadequate and should not be relied upon in making any decisions regarding the approvability of this submission.

(N.B. This Clinical Inspection Summary is based on Inspectional Observations (Form FDA 483) for two sites in the MICA Study, and verbal communications with the FDA field investigator for the one site (Ohio Study). Should the EIRs and exhibits from all sites, when received, contain additional information that would significantly affect the classification or have an impact on the approval process, I will inform the Review Division in an amendment.)

Roy Blay, Ph.D. Good Clinical Practice Branch I, HFD-46 Division of Scientific Investigations

CONCURRENCE:

Khin Maung U. M.D. Branch Chief, Good Clinical Practice Branch I (HFD-46) Division of Scientific Investigations

cc: HFD-540 Doc. Rm. NDA 21-201 HFD-45/Program Management Staff (electronic copy) HFD-46/RF, c/r/f, Blay o:\blay\21201.doc

Conclusion: At this point in time, it appears that data from several subjects at this site can NOT be used in support of the primary efficacy endpoint analysis in NDA 21-201.

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Division of Drug Marketing, Advertising, and Communications

Predecisional Agency Information

Date: May 19, 2004

From: Sonny Saini, Pharm.D. – DDMAC Iris Masucci, Pharm.D. – DDMAC

To: Lea Carrington

Re: NDA 21-201, Aethoxysklerol

<u>General</u>

• Are there any Clinical Studies data to be included in a Clinical Studies Section?

Clinical Pharmacology

- The term (b) (4)", is used in the first paragraph of this section. Is this a medically accurate term? If not, we recommend deleting since, it could be promotional in tone.
- Page 2
 (b) (4)
 (b) (4)
 (b) (4)

This entire paragraph seems more suited for the Information for the Patient section rather than Clinical Pharmacology.

• Page 2

The second paragraph states:			(b) (4)
	(b) (4)		
•			(b) (4)
	u.		
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•		(b) (4) [,]	
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) (4			
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Should this sentence be in a Pharmacokinetics section?

Indications and Usage

• The presentation of the Aethoxysklerol concentrations per varicose vein size seems more appropriate for the Dosage and Administration section. The Indication paragraph already refers the reader there, so it seems unnecessary to give the dosing concentrations here.

Contraindications

•	(b) (4) [,]	
		_

Warnings



We suggest giving the incidence rates of each of these events for completeness. In addition, we are currently discouraging use of the word "pivotal" to describe studies in labeling per the draft guidance on the Clinical Studies section of labeling.



• We suggest use of a typical adverse events table here with incidence rates rather than listing the events in categories of "common," "uncommon," etc.

Dosage and Administration

• (b) (4)

Should this sentence be put elsewhere in this section to avoid its being overlooked? Also, is the word ^{(b) (4)} necessary here?

Animal Toxicology

(b) (4)

The phrase ^{(b) (4)}" is vague and is promotional in tone. We suggest deletion.

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/s/ -----Sonny Saini 5/19/04 10:42:05 AM DDMAC REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office):		FROM:		
of Drug Marketing, Advertising and Communications (DDMAC) م ب-042 PKLN/Room 17B17			HFD-540 Div. of Dermatologic and Dental Drug Products (DDDDP) Lea Carrington, Regulatory Project Manager	
DATE December 31, 2003	NDA No. 21-201		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE May 2004
NAME OF FIRM: Chemische Fabrik Kreuss	ler c/o INC F	Research, Inc.		
		REASON FOR	RREQUEST	
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		V. SCIENTIFIC IN	VESTIGATIONS	
			PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: The Applicant's product is Aethoxysklerol (polidocanol) Injectable, 0.5%, 1% (b) (4) proposed for the indication varicose veins in the lower extremities. The Applicant's proposed label is attached. No carton and immediate container labels have been received. A labeling day has been scheduled for June 30, 2004. Please provide comments in sufficient time prior to meeting. If you have any questions or need additional information, please contact me at 301-827-2072 or email me at carringtonl@cder.fda.gov. Thank you, Lea				
SIGNATURE OF REQUESTER Lea Carrington			METHOD OF DELIVERY (Check one)	HAND
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/s/ Sonny Saini 5/19/04 10:38:04 AM

PROJECTION OF DRUG SAREY ODS - PRUMIN, Room 15B-08, HFD-410 FROJE HFD-40, Div. of Dermatologic and Dental Drug Products DDDDDP) Lea Carrington, Regulatory Project Manager DATE April 22, 2004 NOA No. 21:201 CLASSIFICATION OF DRUG 15 DESIRED COMPLETION DATE June 1, 2004 DATE April 22, 2004 21:201 CLASSIFICATION OF DRUG 15 DESIRED COMPLETION DATE June 1, 2004 NAME OF FRAME. Chemische Fabrick Kraussar- clo INC Research, Inc. EXEMPTION DATE June 1, 2004 DESIRED COMPLETION DATE June 1, 2004 IN REV PROTOCOL PROTO	DEPARTMENT OF HEALTH AND HUMAN SER PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	VICES		REQUEST FOR CONSU	LTATION	
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/s/ Leonthena Carrington 4/22/04 01:06:25 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSUL	TATION		
TO (Division/Office): Sommie Beam, Project Manager & Linda Wisniewski, Safety Evaluator , – Div. of Medication Errors and Technical Support (DMETS), HFD-420 PKLN/Room 6-34			FROM: HFD-540, Div. of Dermatologic and Dental Drug Products (DDDDP) Lea Carrington, Regulatory Project Manager			
DATE January 14, 2004	NDA No. 21-201		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE May 2004		
NAME OF FIRM: Chemische Fabrik Kreuss	ler c/o INC F	Research, Inc.	L	· · · · · ·		
		REASON FOR	RREQUEST			
		I. GENI	ERAL			
Image: New Protocol Image: Protocol Image: Protocol Image: Progress Report Image: Protocol Image: Protocol Image: Progress Report Image: Protocol Image: Protocol Image: Protocol Image: Protocol Image: Protocol			 RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW X OTHER (SPECIFY BELOW): Carton and container label 			
		II. BIOME	ETRICS			
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH			
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER (SPECIEX BELOW)			 □ CHEMISTRY REVIEW □ PHARMACOLOGY □ BIOPHARMACEUTICS □ OTHER (SPECIFY BELOW): 			
ISSOLUTION □ BIOAVAILABILTY STUDIES □ PHASE IV STUDIES			DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST			
		IV. DRUG EX	PERIENCE			
PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS			
		V. SCIENTIFIC IN	VESTIGATIONS	e maanii Maad		
COMMENTS/SPECIAL INSTRUCTIONS:		· · · · · · · · · · · ·				
The Applicant's product is Aethoxysklerol (polidocanol) Injectable, 0.5%, 1%, (b) (4) proposed for the indication varicose veins in the lower extremities. The Applicant's proposed carton and container label is attached. If you have any questions or need additional information, please contact me at 301-827- 2072 or email me at carringtonl@cder.fda.gov.						
Thank you, Lea						
SIGNATURE OF REQUESTER Lea Carrington			METHOD OF DELIVERY (Check one)	HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER			
6 Page(s)	of Draft	Labeling bas bee	n Withheld in Full immedia	tely following		

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

/s/ Leonthena Carrington 1/14/04 10:42:59 AM