CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-201s000

CHEMISTRY REVIEW(S)

NDA 21-201
Quality Review #2 Addendum #2

Polidocanol Injection
0.5% and 1%

Chemische Fabrik Kreussler & Co., GmbH

Wendy I. Wilson-Lee, Ph. D.
Office of New Drug Quality Assessment
For
Division of Cardio-Renal Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-201
2. REVIEW: 02 Addendum #2
3. REVIEW DATE: 17-MAR-2010
4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Memo to File	12-MAR-2010
Quality Review #2 Addendum	06-JAN-2010
Quality Review #2	02-DEC-2009
Incomplete Response Letter	18-AUG-2008
Not Approvable Letter	02-AUG-2004
Quality Review #1	01-JUL-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N/A	N/A

7. NAME & ADDRESS OF APPLICANT:

Name:	Chemische Fabrik Kreussler & Co., GmbH
Address:	Rheingaustrasse 87-93 D-65203 Wiesbaden Germany
Representative:	Howard M. Smith Associate Director, Medical Writing INC Research, Inc. (Official Agent)
Telephone:	434-244-5110

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Asclera™
b) Non-Proprietary Name (USAN): Polidocanol Injection
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)
10. PHARMACOL. CATEGORY: Treatment of varicose veins of the lower extremities
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 0.5%, 1%
13. ROUTE OF ADMINISTRATION: Intravenous

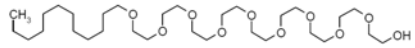
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Polyethylene Glycol Monododecyl Ether
Mol. Formula: $C_{12}H_{25}(OCH_2CH_2)_nOH$, $1 < n \leq 22$
Mol. Weight: 600 (mean)



Shown: n = 9; range in drug substance: 1 < n < 23

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	I	(b) (4)	Facilities and Procedures	2	N/A	-	-
(b) (4)	III	(b) (4)	Type I Glass Ampoules	4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	35,139	Sclerosing therapy of varicose veins

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Approval.	25-NOV-2009	J. Lawrence
EES	**Acceptable**	**17-MAR-2010**	**A. Inyard**
Pharm/Tox	Approval	18-NOV-2009	W. Link
Biopharm	Approval.	25-NOV-2009	P. Hinderling
LNC	N/A	-	-
Methods Validation	Validation by FDA not needed.	10-SEP-2009	W. Wilson
DMEPA	Asclera tradename approved	30-NOV-2009	C. Holquist
EA	Categorical exclusion granted.	10-SEP-2009	W. Wilson
Microbiology	Approval	21-DEC-2009	V. Pawar

List of Tables

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Chemistry Review for NDA 21-201

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend approval of both the 0.5% and 1% strength Asclera™ (polidocanol) Injection drug products, pending labeling. Please include the following two comments in the approval letter:

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

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

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

We have no Phase 4 CMC recommendations.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The US Adopted Name (USAN) for the drug substance is polidocanol, a mixture of homologous polyethylene glycol alkyl ethers having an average extent of polymerization equivalent to nine repeated ethylene glycol units. Polidocanol is a colorless to light-yellow, clear liquid, or it may appear as a white, waxy solid that resembles petrolatum. Polidocanol (b) (4) Polidocanol is a new molecular entity, and has not been previously approved for use as an active pharmaceutical ingredient in the United States. The drug product is a sterile solution, packaged in Type I, sealed glass ampoules, each containing (b) (4) of solution (2 mL nominal), and available in two strengths – 0.5% or 1%. The formulation contains compendial excipients and is sterilized by (b) (4).

B. Description of How the Drug Product is Intended to be Used

The drug product is supplied in single-use vials containing 2 mL (nominal volume) as a (b) (4) sterilized solution. The intended clinical use is for the treatment of varicose veins in the lower limbs. The two strengths of drug product are each intended to treat different levels of severity of the disease. The 0.5% strength is intended for treatment of very small varicose veins (spider veins) ≤ 1 mm in diameter. The 1% strength is indicated for small varicose veins (reticular veins) 1 to 3 mm in diameter. The proposed drug product shelf-life is 36 months when stored at 15-30°C (59-86°F). The drug product is not intended for direct-to-patient marketing and will be marketed only to health care providers due to the intravenous route of administration.

C. Basis for Approvability or Not-Approval Recommendation

On 10-MAR-2010, the Office of Compliance entered an "Acceptable" recommendation for the (b) (4) (b) (4). This "Acceptable" recommendation indicates that all issues concerning the original "Withhold" recommendation on 06-JAN-2010 were adequately addressed and resolved by the facility. On 17-MAR-2010, the Office of Compliance issued an overall recommendation of "Acceptable" for NDA 21-201. As all facilities associated with this NDA have "Acceptable" recommendations, we recommend approval of both the 0.5% and 1% strength Asclera™ (polidocanol) Injection drug products, pending labeling.

III. Administrative

A. Reviewer's Signature

Wendy I. Wilson-Lee

B. Endorsement Block

WWilson-Lee: 17-MAR-2010
KSrinivasachar: 17-MAR-2010
RSood: 18-MAR-2010

C. CC Block

DHenry
MMonteleone

5 Page(s) has 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 & CO. GMBH	Asclera (polidocanol) 0.5%/1%

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/s/

WENDY I WILSON
03/18/2010

RAMESH K SOOD
03/18/2010

INTEROFFICE MEMORANDUM

TO: NDA 21-201

FROM: WENDY I. WILSON-LEE

SUBJECT: UPDATED FACILITY INPSECTION STATUS

DATE: 3/11/2010

CC: KASTURI SRINIVASACHAR, RAMESH SOOD, CHRISTINE MOORE, DON HENRY, MICHAEL MONTELEONE, KHIN U

On 10-March-2010, the Office of Compliance entered an "Acceptable" recommendation for the (b) (4). This "Acceptable" recommendation indicates that all issues concerning the original "Withhold" recommendation on 06-JAN-2010 were adequately addressed and resolved by the facility. As all other facilities associated with this NDA also have "Acceptable" recommendations, we recommend approval of both the 0.5% and 1% strength Asclera™ (polidocanol) Injection drug products, pending labeling. Please include the following two comments in the approval letter:

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

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

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/

WENDY I WILSON
03/11/2010

RAMESH K SOOD
03/12/2010

Asclera™
(polidocanol) Injection
NDA 21-201

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Chemische Fabrik Kreussler & Co., GmbH.
Rheingaustrasse 87-93
D-65203 Wiesbaden
Germany

Indication: Treatment of varicose veins of the lower extremities

Presentation: Injection solution containing either 0.5% or 1.0% polidocanol packaged in 2 mL, Type I, glass ampoules.

EER Status: **Withhold** (06-JAN-10) due to unresolved issues at the drug product manufacturing site

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(b)
Methods Validation – Revalidation by Agency not requested
Microbiology – Approval recommended (V. Pawar, 21-DEC-2009)

Original Submission: 29-Sep-2003
Found to be Not Approvable on 02-Aug-2004**.** The only CMC related deficiencies were microbiological regarding sterilization procedures.

Re-Submission: 10-JUL-2009
The applicant resubmitted on 21-Jun-08, but the resubmission was deemed an incomplete response due to the lack of sterilization information and was refused to file on 18-AUG-2008. The sponsor resubmitted the NDA on 10-JUL-2009, providing a complete response to all issues noted.

The resubmission contains CMC updates and changes for both drug substance and drug product, including changes to specifications and drug product manufacturers. (b) (4)

Post-Approval Agreements: None

Drug Substance:

The drug substance is a mixture of homologous polyethylene glycol alkyl ethers between 1 and 22 monomeric units, having an average extent of polymerization equivalent to nine repeated ethylene glycol units and a mean molecular weight of around 600. The US Adopted Name (USAN) for the drug substance is polidocanol. Polidocanol is a colorless to light-yellow, clear liquid. As its melting point is (b) (4), it may also appear as a white, waxy solid that resembles petrolatum (b) (4)

(b) (4)

The drug substance does not have any stereoisomers. Polidocanol is a new molecular entity,

and has not been previously approved for use as an active pharmaceutical ingredient in the United States.

The bulk drug substance manufacturer is Chemische Fabrik Kreussler & Co., GmbH in Germany. The manufacturing process comprises of (b) (4) .

The drug substance release specification includes testing of appearance, (b) (4) The sponsor established the impurity and degradation profiles for polidocanol. The sponsor adequately characterized the primary reference standard for drug substance, manufactured by commercial process, using the proposed regulatory methods as well as additional methods.

The stability data for three commercial batches support a (b) (4) month retest period for the bulk drug substance stored inside pure aluminum canisters sealed aluminum screw cap closures with (b) (4) sealing rings at controlled room temperature.

Conclusion: Drug substance is acceptable.

Drug Product:

Asclera™ is an injection, available in two strengths – 0.5% and 1.0%. The drug product is an aqueous-alcohol solution containing (b) (4) water for injection, and (b) (4), (b) (4) (b) (4) phosphate and (b) (4) potassium phosphate. All of the excipients comply with USP or NF standards. The drug product does not contain overages.

The drug product manufacturer is (b) (4). The drug product manufacturing process involves four major unit operations – preparation of the bulk solution, filtration, filling, and packaging. (b) (4) The sponsor uses (b) (4). The manufacturing process (b) (4) The methods and equipment used during drug product manufacturing are typical for this dosage form.

The drug product release specification includes testing for appearance, extractable volume, pH, polidocanol (b) (4) The drug product reference standard is the same as that for the drug substance. The proposed regulatory methods are either (b) (4) for their intended purpose.

The stability data support expiration dating of 36 months for all strengths of drug product stored at controlled room temperature conditions [25º C (77º F); excursion permitted to 15-30º C (59-86º F)], in the 2 mL, Type I glass ampoules.

Conclusion: Drug product is acceptable.

Additional Items:

- The sponsor commits to conducting stability testing of the first three (3) commercial batches of each drug product strength with addition of one commercial batch yearly on a rotating principle according to drug product strength, thereafter.

- All associated Drug Master Files are acceptable or the pertinent information was provided in the application.

- The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product.

- The originally proposed tradename of (b) (4) was denied and the tradename of Asclera was approved.

Overall Conclusion:

The application cannot be recommended for approval from a CMC perspective because of Withhold recommendation issued by the Office of Compliance on Jan 6, 2010. There are no other issues from a CMC standpoint.

Christine M. V. Moore, Ph.D.
Director (Acting)
DPA I/ONDQA

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/

CHRISTINE M MOORE
01/08/2010

NDA 21-201
Quality Review #2 Addendum

Polidocanol Injection
0.5% and 1%

Chemische Fabrik Kreussler & Co., GmbH

Wendy I. Wilson-Lee, Ph. D.
Office of New Drug Quality Assessment
For
Division of Cardio-Renal Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-201
2. REVIEW: 02 Addendum
3. REVIEW DATE: 04-JAN-2010
4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Quality Review #2	02-DEC-2009
Incomplete Response Letter	18-AUG-2008
Not Approvable Letter	02-AUG-2004
Quality Review #1	01-JUL-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	06-JAN-2010
Amendment	05-JAN-2010
Amendment	23-DEC-2009
Amendment	09-DEC-2009
Amendment	02-DEC-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Chemische Fabrik Kreussler & Co., GmbH
Address:	Rheingaustrasse 87-93 D-65203 Wiesbaden Germany
Representative:	Howard M. Smith Associate Director, Medical Writing INC Research, Inc. (Official Agent)
Telephone:	434-244-5110

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Asclera™
b) Non-Proprietary Name (USAN): Polidocanol Injection
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)
10. PHARMACOL. CATEGORY: Treatment of varicose veins of the lower extremities
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 0.5%, 1%

13. ROUTE OF ADMINISTRATION: Intravenous

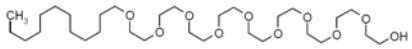
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Polyethylene Glycol Monododecyl Ether
Mol. Formula: $C_{12}H_{25}(OCH_2CH_2)_nOH$, $1 < n \leq 22$
Mol. Weight: 600 (mean)



Shown: n = 9; range in drug substance: 1 < n < 23

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	I	(b) (4)	Facilities and Procedures	2	N/A	-	-
(b) (4)	III	(b) (4)	Type I Glass Ampoules	4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
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7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	35,139	Sclerosing therapy of varicose veins

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Approval.	25-NOV-2009	J. Lawrence
EES	Pending.		
Pharm/Tox	Approval	18-NOV-2009	W. Link
Biopharm	Approval.	25-NOV-2009	P. Hinderling
LNC	N/A	-	-
Methods Validation	Validation by FDA not needed.	10-SEP-2009	W. Wilson
DMEPA	Asclera tradename approved	30-NOV-2009	C. Holquist
EA	Categorical exclusion granted.	10-SEP-2009	W. Wilson
Microbiology	Approval	21-DEC-2009	V. Pawar

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Chemistry Review for NDA 21-201

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend a complete response action for the 0.5% and 0.1% Polidocanol Injection packaged in 2 mL, Type I, glass ampoules based on a withhold recommendation from the Office of Compliance for the drug product manufacturer on 06-JAN-2010.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

We have no Phase 4 CMC recommendations.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The US Adopted Name (USAN) for the drug substance is polidocanol, a mixture of homologous polyethylene glycol alkyl ethers having an average extent of polymerization equivalent to nine repeated ethylene glycol units. Polidocanol is a colorless to light-yellow, clear liquid, or it may appear as a white, waxy solid that resembles petrolatum. (b) (4) . Polidocanol is a new molecular entity, and has not been previously approved for use as an active pharmaceutical ingredient in the United States. The drug product is a sterile solution, packaged in Type I, sealed glass ampoules, each containing (b) (4) mL of solution (2 mL nominal), and available in two strengths – 0.5% or 1%. The formulation contains compendial excipients and is sterilized by (b) (4).

B. Description of How the Drug Product is Intended to be Used

The drug product is supplied in single-use vials containing 2 mL (nominal volume) as a (b) (4) sterilized solution. The intended clinical use is for the treatment of varicose veins in the lower limbs. The two strengths of drug product are each intended to treat different levels of severity of the disease. The 0.5% strength is intended for treatment of very small varicose veins (spider veins) ≤ 1 mm in diameter. The 1% strength is indicated for small varicose veins (reticular veins) 1 to 3 mm in diameter. The proposed drug product shelf-life is 36 months when stored at 15-30°C (59-86°F). The drug product is not intended for direct-to-patient marketing and will be marketed only to health care providers due to the intravenous route of administration.

C. Basis for Approvability or Not-Approval Recommendation

We recommend a complete response action for the 0.5% and 0.1% Polidocanol Injection packaged in 2 mL, Type I, glass ampoules based on a withhold recommendation from the Office of Compliance for the drug product manufacturer on 06-JAN-2010. In addition, the recommendations for the drug substance manufacturer and the drug substance stability tester are pending as of 06-JAN-2010. Thus, the overall recommendation for the application is pending as of 06-JAN-2010.

III. Administrative

A. Reviewer's Signature

Wendy I. Wilson-Lee

B. Endorsement Block

WWilson-Lee: 06-JAN-2010
KSrinivasachar: 06-JAN-2010
RSood: 06-JAN-2010

C. CC Block

DHenry
MMonteleone

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

WENDY I WILSON
01/06/2010

RAMESH K SOOD
01/06/2010

NDA 21-201

Polidocanol Injection
0.5% and 1%

Chemische Fabrik Kreussler & Co., GmbH

Wendy I. Wilson-Lee, Ph. D.
Office of New Drug Quality Assessment
For
Division of Cardio-Renal Drug Products

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1. NDA: 21-201
2. REVIEW: 02
3. REVIEW DATE: 02-DEC-2009
4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Incomplete Response Letter	18-AUG-2008
Not Approvable Letter	02-AUG-2004
Quality Review #1	01-JUL-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	12-NOV-2009
Amendment	19-AUG-2009
Amendment	10-JUL-2009
Amendment	21-JUL-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Chemische Fabrik Kreussler & Co., GmbH
Address:	Rheingaustrasse 87-93 D-65203 Wiesbaden Germany
Representative:	Howard M. Smith Associate Director, Medical Writing INC Research, Inc. (Official Agent)
Telephone:	804-556-6357

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Asclera™
b) Non-Proprietary Name (USAN): Polidocanol Injection
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)
10. PHARMACOL. CATEGORY: Treatment of varicose veins of the lower extremities
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 0.5%, 1%
13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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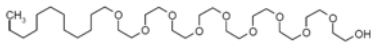
Chemical Name: Polyethylene Glycol Monododecyl Ether
Mol. Formula: $C_{12}H_{25}(OCH_2CH_2)_nOH$, $1 < n \leq 22$
Mol. Weight: 600 (mean)



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Pharm/Tox	Approval	18-NOV-2009	W. Link
Biopharm	Pending.	25-NOV-2009	P. Hinderling
LNC	N/A	-	-
Methods Validation	Validation by FDA not needed.	10-SEP-2009	W. Wilson
DMEPA	Proposed tradename ((b) (4)) denied. Asclera tradename approved	16-JUL-2009 30-NOV-2009	C. Holquist
EA	Categorical exclusion granted.	10-SEP-2009	W. Wilson
Microbiology	Approvable, pending one issue.	30-NOV-2009	V. Pawar

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I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend approval – pending labeling, resolution of the microbiology issue, and inspection of manufacturing facilities – of the 0.5% and 0.1% Polidocanol Injection packaged in 2 mL, Type I, glass ampoules. We grant a (b) (4) month retest period for the drug substance and a 36 month expiry for both strengths of the drug product when stored at USP controlled room temperature [15-30ºC (59-86ºF)] in the approved container closure system.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

We have no Phase 4 CMC recommendations.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The US Adopted Name (USAN) for the drug substance is polidocanol, a mixture of homologous polyethylene glycol alkyl ethers having an average extent of polymerization equivalent to nine repeated ethylene glycol units. Polidocanol is a colorless to light-yellow, clear liquid, or it may appear as a white, waxy solid that resembles petrolatum. (b) (4) . Polidocanol is a new molecular entity, and has not been previously approved for use as an active pharmaceutical ingredient in the United States. The drug product is a sterile solution, packaged in Type I, sealed glass ampoules, each containing (b) (4) mL of solution (2 mL nominal), and available in two strengths – 0.5% or 1%. The formulation contains compendial excipients and is sterilized by (b) (4)

B. Description of How the Drug Product is Intended to be Used

The drug product is supplied in single-use vials containing 2 mL (nominal volume) as a (b) (4) sterilized solution. The intended clinical use is for the treatment of varicose veins in the lower limbs. The two strengths of drug product are each intended to treat different levels of severity of the disease. The 0.5% strength is intended for treatment of very small varicose veins (spider veins) ≤ 1 mm in diameter. The 1% strength is indicated for small varicose veins (reticular veins) 1 to 3 mm in diameter. The proposed drug product shelf-life is 36 months when stored at 15-30°C (59-86°F). The drug product is not intended for direct-to-patient marketing and will be marketed only to health care providers due to the intravenous route of administration.

C. Basis for Approvability or Not-Approval Recommendation

We recommend approval – pending labeling, resolution of the microbiology issue, and inspection of manufacturing facilities – of the 0.5% and 0.1% Polidocanol Injection packaged in 2 mL, Type I, glass ampoules. The chemistry, manufacturing, and controls information provided in the resubmission and

subsequent amendments support the approval of this application. The drug substance and drug product regulatory specifications adequately control the identity, purity, strength, and quality of each. The drug substance and drug product stability data demonstrate that both remain stable through the proposed re-test and expiry periods. The drug substance and drug product container closures provide adequate protection to ensure the stability of both. The labeling adequately provides the storage conditions, expiry, ingredient, and how supplied information.

As of 02-DEC-2009, the Office of Compliance has not issued a final recommendation on the acceptability of the manufacturing facilities. In addition, the microbiology review team identified an additional issue on 30-NOV-2009 regarding sterility of the drug product. We will file a final CMC approvability recommendation memo once these issues are resolved.

III. Administrative

A. Reviewer's Signature

Wendy I. Wilson-Lee

B. Endorsement Block

WWilson-Lee: 02-DEC-2009
KSrinivasachar: 02-DEC-2009
RSood: 02-DEC-2009

C. CC Block

DHenry
MMonteleone

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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/

WENDY I WILSON
12/02/2009

RAMESH K SOOD
12/03/2009

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	21-201
Applicant:	Chemische Fabrik Kruessler & Co., GmbH
Letter Date:	21 July 2008
Stamp Date:	21 July 2008
PDUFA Date:	21 Jan. 2009
Tradename:	(b) (4)
Established Name:	Polidocanol
Dosage Form:	Sterile solution (injection), 0.5%, 1%
Route of Administration:	Intravenous
Indication:	Treatment of varicose veins of the lower extremity
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	To be determined

Summary

This is a resubmission of the original NDA which was issued a "Not Approvable" letter on Aug. 2, 2004 by the Division of Dermatologic and Dental Drug Products. This drug has been transferred to the Division of Cardiovascular and Renal Products. The only CMC related deficiencies listed in the letter pertained to microbiology; specifically, the controls were considered inadequate to prevent microorganisms surviving the sterilization procedures for the product. The CMC review #1 dated July 13, 2004 also lists some deficiencies concerning the postapproval stability commitment and labeling which were apparently not communicated to the Applicant. It should be noted that this review is not in DFS – a copy was obtained from the reviewer, Joel Hathaway.

The resubmission contains CMC updates and changes for both drug substance and drug product that need to be reviewed. New lots of drug substance have been manufactured and release and stability data for these have been submitted. (b) (4) The initial manufacturer of the product was (b) (4) but this was changed to (b) (4) (b) (4) in the original NDA submission. In this resubmission, manufacturing has been transferred back to (b) (4). It is stated that during all these transfers no change in process and controls have occurred. (b) (4) will be manufacturing the product at a new facility which is adjacent to the old one. Minor specification changes are proposed and new batches have been manufactured at the (b) (4) site in 2006 and 2007. Release and stability data for these have been provided in addition to supporting stability data from (b) (4).

Comments and Recommendations

Since the NA letter issued in 2004 cited only microbiology deficiencies, the completeness of the response should be assessed by the microbiology reviewer and a consult request should be generated for the microbiology review. Manufacturing, testing and packaging facilities should be re-entered into EES because the original overall recommendation was in 2004. It should be noted that the establishment information attached to Form 356h does not seem to be complete

and testing sites are listed elsewhere in the submission. Also, some sites are different form the original, including (b) (4) which has a different registration number. A single CMC reviewer is recommended for this application since only CMC changes and updates need to be reviewed.

Kasturi Srinivasachar	Aug.7, 2008
Pharmaceutical Assessment Lead	Date
Ramesh Sood, Ph.D.	Aug. 7, 2008
Branch Chief	Date

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/s/

Kasturi Srinivasachar
8/7/2008 09:59:52 AM
CHEMIST

Ramesh Sood
8/7/2008 12:40:43 PM
CHEMIST

NDA 21-201

Aethoxysklerol® (polidocanol) Injection
0.5%, 1% (b) (4)

Chemische Fabrik Kreussler &Co., GmbH

Joel S. Hathaway, Ph.D.
Division of Dermatologic and Dental Drug Products

HFD-540

Review #1

July 13, 2004

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-201

2. REVIEW #: 1

3. REVIEW DATE: July 1, 2004

4. REVIEWER: Joel S. Hathaway, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original N-000	02-OCT-2003
Amendment N-000 (BC)	24-NOV-2003
Amendment N-000 (BB)	09-DEC-2003
Amendment N-000 (C)	23-DEC-2003
Amendment N-000 (BC)	29-JAN-2004
Amendment N-000 (BL)	07-APR-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Chemische Fabrik Kreussler & Co., GmbH
Address:	Rheiningaustrasse 87-93 D-65203 Wiesbaden Germany
Representative:	INC Research, Inc. Howard M. Smith, Sr. Director Regulatory Operations and Medical Writing 675 Peter Jefferson Highway Suite 120 Charlottesville, VA 22911
Telephone:	(434) 244-5165 (434) 295-7209 (fax)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Aethoxysklerol
b) Non-Proprietary Name (USAN): polidocanol
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)

10. PHARMACOLOGIC CATEGORY: sclerosant

11. DOSAGE FORM: Sterile solution for intravenous injection: Injection

12. STRENGTH/POTENCY: 0.5%, 1% (b) (4)

13. ROUTE OF ADMINISTRATION: Intravenous injection

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

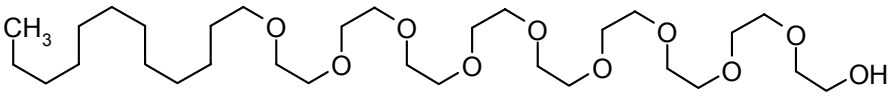
_____ SPOTS product – Form Completed

___X___ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Established Name: polidocanol
Code Name(s): N/A
Trade Name(s): Laureth 9, Lauromacrogol 400
Chemical Names (b) (4)

Molecular Formula: $C_{30}H_{62}O_{10}$ (for n=9)
Molecular Weight: 582.82 (for n=9)
Shown: for n = 9; range in drug substance: $1 < n < 23$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	I	(b) (4)	Facilities and procedures	2	N/A	N/A	Not reviewed; Type I DMF
(b) (4)	III	(b) (4)	Type I Glass Ampoules	1	Adequate	12-JUL-2004	Previously reviewed - adequate; no significant changes or updates since last review 19-SEP-2001

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	35,139	Supporting IND

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Approvable (NA)?	03-JUN-2004	Steve Thomson (HFD-725)
EES	Withhold Approval	26-JUL-2004	S. Adams(HFD-322)
Pharm/Tox	Approvable (AE)	28-APR-2004	Norman A. See, PhD (HFD-540)
LNC			
Methods Validation	Pending		

Chemistry Review Data Sheet

ODS/DMETS	Acceptable	05-MAR-2004	Linda M. Wisniewski, RN (HFD-420)
EA	Categorical Exclusion	30-JUN-2004	J. S. Hathaway, PhD (HFD-830)
Microbiology	Approvable (AE) (See Executive Summary, Section C.)	17-JUN-2004	Stephen E. Langille, PhD (HFD-805)

The Chemistry Review for NDA 21-201

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

A recommendation of "Approvable" may be made at this time for the chemistry, manufacturing and controls (CMC) information as submitted in the NDA application and supporting amendments. The following issues are to be addressed by the applicant before approval can be recommended.

The reviewer of the CMC Microbiological information in the NDA has recommended this NDA as "Approvable". The CMC Micro review identified five deficiencies in the microbiological validation, processing and controls procedures used in the drug product manufacturing process. These are listed below, in Section C.

The inspection report by the Office of Compliance recommended approval on 07-OCT-2004.

The CMC review of the NDA identified items and changes recommended for incorporation into labeling, as noted in the review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The US Adopted Name (USAN) for the drug substance in Aethoxysklerol® is polidocanol, a mixture of homologous polyethylene glycol alkyl ethers having an average extent of polymerization equivalent to nine repeated ethylene glycol units. Polidocanol is a colorless to light-yellow, clear liquid, or it may appear as a white, waxy solid that resembles petrolatum. (b) (4) Polidocanol is a new molecular entity, and has not been previously approved for use as an active pharmaceutical ingredient in the United States.

The drug products are sterile solutions packaged in sealed glass ampoules, each containing approximately (b) (4) mL of solution (2 mL nominal), and available in three strengths: 0.5%, 1% (b) (4)

B. Description of How the Drug Product is Intended to be Used

The drug product, Aethoxysklerol® (polidocanol) Injection, 0.5%, 1% (b) (4) is supplied in single-use vials containing 2 mL (nominal volume) as a (b) (4) sterilized solution. The intended clinical use is for the treatment of varicose veins in the lower limbs. The (b) (4) strengths of drug product are each intended to treat different levels of severity of the disease. The 0.5% strength is intended for treatment of very small varicose veins (spider veins) ≤1 mm in diameter, the 1% strength is indicated for small varicose veins 1 to 3 mm in diameter, (b) (4) The proposed shelf-life for Aethoxysklerol® (polidocanol) Injection is 36 months when stored at 15-30°C (59-86°F).

The drug products are not intended to be marketed directly to patients, but only to health care providers, since they must be administered by intravenous injection.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provide adequate information on the chemistry, manufacturing and controls for the production of Aethoxysklerol® (polidocanol injection), 0.5%, 15 (b) (4) However, pre-approval inspection for cGMP compliance at the drug substance manufacturing, testing and packaging facility has resulted in a recommendation, by the Office of Compliance, to withhold approval at this time. No recommendation for approval can be made pending the issuance of a satisfactory inspection report by the Office of Compliance.

The CMC Microbiology reviewer has identified five deficiencies in the microbiological validation, processing and controls procedures used in the drug product manufacturing process, and has recommended an "Approvable" action. The following are the approvability issues identified by the CMC-Micro reviewer.

1. Please provide the methods used to control and monitor production sterilization cycles in the (b) (4).
2. Please provide a statement as to whether or not the product will be reprocessed.
3. Please provide an adequate description or diagram of (b) (4) or biological indicator placement within the validation load.
4. Please provide a statement as to whether or not the biological indicators were placed directly into the drug product (b) (4). The D-value of

the biological indicators in the drug product or master solution should be provided to prove that the sterilization cycle has been adequately validated.

5. Please provide incubation parameters for the biological indicators after sterilization validation cycles.

In addition, this CMC reviewer also recommends an "Approvable" action, and that the applicant agree to (1) revisions of the post-approval stability commitment, and (2) the incorporation of recommended labeling changes, as noted in the review.

III. Administrative

A. Reviewer's Signature

(See attached electronic signature page)

_____

Joel S. Hathaway, Ph.D.

B. Endorsement Block

JSHathaway/Date: 13-JUL-2004
ChemistryTeamLeader/
ProjectManager/FHCross/

C. CC Block

In DFS.

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/s/

Steve Hathaway
8/13/2008 11:46:55 AM
CHEMIST
Original NDA review - Missing in DFS; (re)submitted

NDA FILEABILITY CHECKLIST

NDA Number: 21-201 **Drug Name:** Aethoxysklerol (polidocanol) 0.5%, 1.0%, (b) (4)
Applicant: Chemische Fabrik Kreussler & Co., GmbH

IS THE CMC SECTION OF THIS APPLICATION FILEABLE? No ___ Yes X

Table 1 Fileability Checklist

The following parameters are necessary for initiating a full review, e.g. complete enough for review but may have deficiencies.

	PARAMETER	YES	NO	COMMENT
1	Is the NDA organized adequately for its CMC content?	X		
2	Are the CMC sections adequately indexed & paginated?	X		
3	Are the CMC sections legible?	X		
4	Are all facilities identified with full street addresses, contact names & CFN #s?		X	
5	Is there a statement that all facilities are prepared for GMP inspections?	X		**cover letter**
6	Has an environmental assessment or categorical exclusion been provided?	X		**Vol. 14**
7	Does the drug substance section contain controls?	X		**Vol. 5.3, tabs 6-7**
8	Does the drug product section contain controls?	X		**Vol. 5.4, tab 8, etc.**
9	Have stability data been submitted to justify the requested expiry date?	X		**see tables on next page; 36 months expiry proposed, stored at 15-30°C**
10	Has the applicant provided all requested data by the division during the IND & pre-NDA phases?	X		**see Vol. 5.30, pp. 26-32**
11	Have draft container labels been provided?		X	
12	Has a draft package insert been provided?	X		**Volume 2; p.i. only**
13	Has an Investigational Formulations section been included?	X		**Volume 14**
14	Are there three Methods Validation documents?		X	**Volumes 15-17**
15	Is a statistical consult required?	X		**possibly?**
16	Is there a separate microbiological section? Is a micro consult required?	X		

Table 2a. STABILITY DATA REQUIRED FOR FILEABILITY (0.5%)

	STABILITY DATA REQUESTED	YES	NO
1	Does the NDA include 12 or more months of stability data?	X	
2	Do the stability data cover the expiry date?	X	
3	Do the stability data include **only** the largest & smallest container sizes?	**n/a**	
4	Do the stability data include all package sizes?	X	
5	Are there tabular data for each size and batch?	X	
6	Are there graphical data for each size and batch?		X
7	Is a statistical consult required?	X	
8	Is a stability protocol included?	X	
9	Are the stability-indicating assays described?	X	
10	Is there a three-point stability commitment?	X	
	Comments: 3 lots from (b) (4), 2 mL ampoules, batch size (b) (4) ampoules, studied through 60 months at RT; 2 lots from (b) (4), 2 mL ampoules, batch size (b) (4) ampoules, studied through 6 months at RT; DOM 10/2002; see vol. 5.5, tab 10, pp. 1031 *et seq.*; 36 month expiry is proposed; **UPDATE NEEDED**		

Table 2b. STABILITY DATA REQUIRED FOR FILEABILITY (1.0%)

	STABILITY DATA REQUESTED	YES	NO
1	Does the NDA include 12 or more months of stability data?		X
2	Do the stability data cover the expiry date?		X
3	Do the stability data include **only** the largest & smallest container sizes?	**n/a**	
4	Do the stability data include all package sizes?	X	
5	Are there tabular data for each size and batch?	X	
6	Are there graphical data for each size and batch?		X
7	Is a statistical consult required?		X
8	Is a stability protocol included?	X	
9	Are the stability-indicating assays described?	X	
10	Is there a three-point stability commitment?	X	
	Comments: no lots from (b) (4) per 1/11/98 meeting; 1 lot from (b) (4) per pre-NDA, 2 mL ampoules, one full scale batch, studied through 6 months at RT; DOM 10/2002; see vol. 5.7, tab 10, pp. 1769 *et seq.*; 36 month expiry is proposed; **UPDATE NEEDED**		

(b) (4)

[redacted]

Table 3 DMF INFORMATION

DMF #	DMF HOLDER	TYPE	LOA DATE	DATE OF LAST REVIEW
(b) (4)	(b) (4)	I	11/9/96	n/a
(b) (4)	(b) (4)	III	6/5/03	9/21/01

Estimated Review Completion Date: May 1, 2004

_____
Review Chemist

_____
Wilson H. DeCamp, Ph.D.
Chemistry Team Leader

Attachment
Cc: NDA
HFD-540/Division File
HFD-540/Chm/
HFD-540/ChmTL/
HFD-540/ProjMgr/
HFD-830/DivDir/

Information requests

1. Please provide two additional copies of the methods validation package (volumes 15-17). Because they are not subject to our validation, the following may be omitted from these copies for compactness, and should be replaced with a single page indicating the page number range of the omitted pages:
    a. all specifications and analytical methods for materials used in the synthesis of polidocanol;
    b. all validation reports for these methods;
    c. all specifications and analytical methods for raw materials used in the manufacturing of all strengths of the finished drug product; and
    d. all in-process test procedures.
2. Please propose an appropriate limit for (b) (4) in the drug product. This should be supported by data and your reasoning for the proposed limit. Based on comments from our pharmacologists, some persons have hypersensitivity to (b) (4).
3. Please provide an estimate of the date on which you will be able to submit the 9- and 12-month stability updates for the lots of the drug product manufactured at (b) (4)
4. Please clarify whether the primary stability batches are only those manufactured by (b) (4), or if they include those manufactured by (b) (4).
5. If the batches manufactured by (b) (4) are to be considered as primary stability batches for our review, please verify that this facility is ready for inspection.
6. Please submit a report of the validation of the ampoule sealing (container and closure system integrity).
7. Please submit a validation summary of the bioburden reduction process (*i.e.*, the (b) (4)). A description of media fill methods and data summaries would adequately address this.
8. The drug substance testing facility identified as (b) (4) appears to also be known as (b) (4), which is located at the exact same address. Are they the same?

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/s/

Steve Hathaway
2/18/04 09:38:11 AM
CHEMIST
Filable - Information requested
For your concurrence

Wilson H. DeCamp
2/18/04 02:49:21 PM
CHEMIST
concur; application may be filed