

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205098Orig1s000

CHEMISTRY REVIEW(S)

NDA 205098
Review #1 Addendum 2

Polidocanol Injectable Foam

Provensis Ltd.

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

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Chemistry Review Data Sheet

1. NDA: 205098
2. REVIEW: 01 Addendum #2
3. REVIEW DATE: 25-NOV-2013
4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Review #1 Addendum #1	07-NOV-2013
Review #1	30-AUG-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (SD 51)	25-NOV-2013
Amendment (SD 50)	25-NOV-2013
Amendment (SD 49)	22-NOV-2013
Amendment (SD 48)	13-NOV-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Provensis Ltd

Address: 5 Fleet Place
London, UK EC4M 7RD
US Agent
BTG International, Inc.
Five Tower Bridge Suite 800
West Conshohocken, PA 19428

Representative: Andrea Collier
Vice President, Regulatory Affairs
215-317-0264 (p)
610-278-1605 (f)

Telephone:

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Varithena®
- b) Non-Proprietary Name (USAN): Laureth 9
- c) Code Name/# (ONDQA only): PEM
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: S

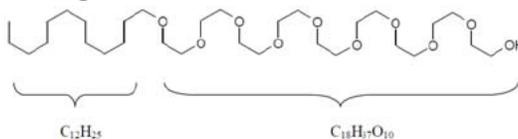
9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Sclerosant

Executive Summary Section

11. DOSAGE FORM: Injectable Foam
12. STRENGTH/POTENCY: 1%
13. ROUTE OF ADMINISTRATION: Intravenous
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Polyethylene Glycol Monododecyl Ether
Mol. Formula: C₃₀H₆₂O₁₀
Mol. Weight: 582.9 (average of 9-mole adduct)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	CODE ¹	STATUS ²	REVIEW DATE	COMMENTS (b) (4)
	III			4	N/A	-	
	III			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	63420	Sclerosant for the treatment of moderate to severe varicose veins

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	-	-	-
EES	Acceptable.	22-NOV-2013	V. Shah & S. Hertz
Pharm/Tox	Approval.	05-SEP-2013	W. Link
Biopharm	No biowaivers needed.	18-MAR-2013	B. Zolnik

Executive Summary Section

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
LNC	(b) (4) as dosage form not acceptable. Recommended dosage form – injectable foam.	16-OCT-2013	Y. Mille & R. Lostritto
Methods Validation	Not required.	24-AUG-2013	W. Wilson-Lee
DMEPA	Varithena trade name acceptable. Recommended changes to carton and container labels and Instructions for Use.	01-OCT-2013	K. DeFrantz
EA	Categorical exclusion granted.	24-AUG-2013	W. Wilson-Lee
Microbiology	Approval.	12-SEP-2013	S. Langille
CDRH – Device	No concerns regarding device design or microfoam generation.	08-AUG-2013	J. Banik
CDRH – Chem. & Mat. Sci	No chemical-device interactions noted.	29-JUL-2013	M. McDermott
CDRH – Human Factors	No additional concerns regarding HF study.	14-NOV-2013	Q. Nguyen

Chemistry Review for NDA 205098

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend approval, pending labeling, of NDA 205098 for polidocanol injectable foam 1% stored in the commercial packaging according to recommended storage conditions.

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

There are no product quality Phase 4 agreements.

II. Summary of Chemistry Assessments

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

Polidocanol is 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 is very soluble in methanol, ethanol, acetone diethyl ether and chloroform, and is freely soluble in water.

The regulatory drug substance specification control

(b) (4)

All drug substance analytical procedures are appropriate and validated for their intended use. Based on the drug substance stability data and in accordance with ICH Q1E, we grant a (b) (4) retest period for polidocanol drug substance stored at (b) (4)

The drug product is a bi-canister, drug-device combination product that produces foam for intravenous administration once activated. One canister contains a (b) (4) polidocanol solution that contains compendial excipients. The other (b) (4) canister contains pressurized oxygen that is used to generate the foam after activation. (b) (4)

Each drug product is supplied as follows:

- A Tyvek pouch containing two sterile (b) (4) mL aluminum alloy canisters connected as a bi-canister system; one canister contains the (b) (4) polidocanol solution; the other canister contains pressurized oxygen.

Executive Summary Section

- Three foam transfer units used to dispense the foam from the canister
- Three administration boxes, each containing three, 10 mL silicone-free Luer syringes; a 20-inch manometer tube; and two compression pads.

The regulatory drug product specification for the bi-canister drug product before activation controls appearance of device (visual) and gas pressure of each pressurized canister. The regulatory drug product specification for the bi-canister drug product after activation controls appearance of foam (visual); visible particulates (visual); sub-visible particulates; foam density ((b) (4)); foam half separation time (b) (4); bubble size (b) (4); extractable volume (b) (4); identity ((b) (4)); pH of solution (b) (4); assay (b) (4); related substances (b) (4); sterility; endotoxin level (b) (4); and content uniformity.

All drug product analytical procedures are appropriate and validated for their intended use. Based on the drug product stability data and in accordance with ICH Q1E, we grant an 18 month expiration date for 1% strength polidocanol injectable foam stored at controlled room temperature in the commercial packaging. OPS Microbiology found the proposed seven (7) day in-use period acceptable with modification of the instructions for use and training materials

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

The proposed indication is the treatment of incompetent great saphenous veins, accessory saphenous veins, and visible varicosities of the great saphenous vein system above and below the knee. The drug product is administered by a trained physician in the office and is not intended for direct use by the patient. The foam remains coherent upon administration and displaces the blood in the vein. The foam is also highly echogenic, allowing for ultrasound-guided administration of the drug product. This allows for controlled treatment of the incompetent vein segment.

The foam is produced using an aqueous solution containing polidocanol at a concentration of 1% w/v and a gas mixture consisting of oxygen/carbon dioxide (65:35) with low nitrogen content. The foam is formulated in a system designed to create consistent physical foam characteristics while allowing for rapid bubble absorption following injection into the vein. The foam transfer unit is attached to the polidocanol canister after activation.

The product is dispensed via a sterile container system that produces foam of consistent, controlled density and bubble size (median bubble diameter < 100 micrometers (µm) and no bubbles > 500 µm) at the time of use. The product is designed to dispense sufficient foam to treat multiple patients during the course of the proposed in-use shelf life. Each canister generates 90 mL of foam. The volume of foam to be injected depends on the size and extent of the veins to be treated. The maximum recommended volume per treatment session is 15 mL, comprising individual injections up to 5 mL each. Generation of foam for each injection requires purging of (b) (4) 5 mL of foam prior to dispensing for use. After allocating for the required purge volume, each canister generates 45 mL of foam for treatment. At the end of a treatment session, the medical professional may store the drug product with the current foam transfer unit for a time not to exceed the approved in-use period. A new foam transfer unit is used for each treatment session. Each administration kit allows for up to three treatment sessions per box.

C. Basis for Approvability or Not-Approval Recommendation

Executive Summary Section

We recommend approval, pending final labeling, of NDA 205098. The applicant adequately responded to all product quality deficiency comments. The revised drug product content uniformity test provides assurance of the drug product content uniformity across canisters in a given batch, across drug product batches, and through the canister life. The revised carton and container labels include all recommended changes. Finally, the overall facilities recommendation from the Office of Compliance is acceptable. Based on these factors, we recommend approval, pending final labeling.

III. Administrative**A. Reviewer's Signature**

Wendy I. Wilson-Lee

Wendy I. Wilson-Lee, Ph.D.

B. Endorsement Block

WWilsonLee: 25-NOV-2013

KSrinivasachar: 25-NOV-2013

OStephens: 25-NOV-2013

C. CC Block

TBouie

MMonteleone

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/s/

WENDY I WILSON-LEE
11/25/2013

OLEN M STEPHENS
11/25/2013

NDA 205098
Review #1 Addendum 1

Polidocanol Injectable Foam

Provensis Ltd.

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

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Chemistry Review Data Sheet

1. NDA: 205098
2. REVIEW: 01 Addendum
3. REVIEW DATE: 04-NOV-2013
4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Review #1

Document Date

30-AUG-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment (SD 47)
Amendment (SD 46)
Amendment (SD 44)
Amendment (SD 43)
Amendment (SD 41)
Amendment (SD 40)
Amendment (SD 37)
Amendment (SD 36)
Amendment (SD 35)

Document Date

23-OCT-2013
22-OCT-2013
14-OCT-2013
24-SEP-2013
20-SEP-2013
19-SEP-2013
03-SEP-2013
28-AUG-2013
07-AUG-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Provensis Ltd

Address: 5 Fleet Place
London, UK EC4M 7RD
US Agent
BTG International, Inc.
Five Tower Bridge Suite 800
West Conshohocken, PA 19428

Representative: Andrea Collier
Vice President, Regulatory Affairs

Telephone: 215-317-0264 (p)
610-278-1605 (f)

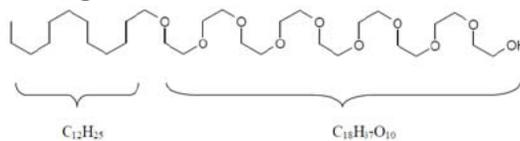
8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Varithena®
- b) Non-Proprietary Name (USAN): Laureth 9
- c) Code Name/# (ONDQA only): PEM
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: S

Executive Summary Section

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Sclerosant
11. DOSAGE FORM: Injectable Foam
12. STRENGTH/POTENCY: 1%
13. ROUTE OF ADMINISTRATION: Intravenous
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Polyethylene Glycol Monododecyl Ether
 Mol. Formula: $C_{30}H_{62}O_{10}$
 Mol. Weight: 582.9 (average of 9-mole adduct)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	REVIEW DATE	COMMENTS
(b) (4)	III		(b) (4)	4	N/A	-	(b) (4)
	III			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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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	63420	Sclerosant for the treatment of moderate to severe varicose veins

Executive Summary Section

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	-	-	-
EES	Pending.	-	V. Shah & S. Hertz
Pharm/Tox	Approval.	05-SEP-2013	W. Link
Biopharm	No biowaivers needed.	18-MAR-2013	B. Zolnik
LNC	(b) (4) as dosage form not acceptable. Recommended dosage form – injectable foam.	16-OCT-2013	Y. Mille & R. Lostritto
Methods Validation	Not required.	24-AUG-2013	W. Wilson-Lee
DMEPA	Varithena trade name acceptable. Recommended changes to carton and container labels and Instructions for Use.	01-OCT-2013	K. DeFrantz
EA	Categorical exclusion granted.	24-AUG-2013	W. Wilson-Lee
Microbiology	Approval.	12-SEP-2013	S. Langille
CDRH – Device	No concerns regarding device design or microfoam generation.	08-AUG-2013	J. Banik
CDRH – Chem. & Mat. Sci	No chemical-device interactions noted.	29-JUL-2013	M. McDermott
CDRH – Human Factors	One deficiency identified. Final recommendation pending.	17-OCT-2013	Q. Nguyen

Chemistry Review for NDA 205098

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend a complete response action for NDA 205098 for polidocanol injectable foam 1% stored in the commercial packaging according to recommended storage conditions.

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

There are no product quality Phase 4 agreements.

II. Summary of Chemistry Assessments

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

Polidocanol is 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 is very soluble in methanol, ethanol, acetone diethyl ether and chloroform, and is freely soluble in water.

The regulatory drug substance specification controls

(b) (4)

(b) (4)

All drug substance analytical procedures are appropriate and validated for their intended use. Based on the drug substance stability data and in accordance with ICH Q1E, we grant a (b) (4) retest period for polidocanol drug substance stored at (b) (4)

The drug product is a bi-canister, drug-device combination product that produces foam for intravenous administration once activated. One canister contains a (b) (4) polidocanol solution that contains compendial excipients. The other (b) (4) canister contains pressurized oxygen that is used to generate the foam after activation. (b) (4)

Each drug product is supplied as follows:

Executive Summary Section

- A Tyvek pouch containing two sterile (b) (4) mL aluminum alloy canisters connected as a bi-canister system; one canister contains the (b) (4) povidone iodine solution; the other canister contains pressurized oxygen.
- Three foam transfer units used to dispense the foam from the canister
- Three administration boxes, each containing three, 10 mL silicone-free Luer syringes; a 20-inch manometer tube; and two compression pads.

The regulatory drug product specification for the bi-canister drug product before activation controls appearance of device (visual) and gas pressure of each pressurized canister. The regulatory drug product specification for the bi-canister drug product after activation controls appearance of foam (visual); visible particulates (visual); sub-visible particulates; foam density (b) (4); foam half separation time (b) (4); bubble size (b) (4); extractable volume (b) (4); identity (b) (4); pH of solution (b) (4); assay (b) (4); related substances (b) (4); sterility; endotoxin level (b) (4); and content uniformity.

All drug product analytical procedures, with the exception of content uniformity, are appropriate and validated for their intended use. Based on the drug product stability data and in accordance with ICH Q1E, we grant an 18 month expiration date for 1% strength povidone iodine injectable foam stored at controlled room temperature in the commercial packaging. OPS Microbiology found the proposed seven (7) day in-use period acceptable with modification of the instructions for use and training materials

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

The proposed indication is the treatment of incompetent great saphenous veins, accessory saphenous veins, and visible varicosities of the great saphenous vein system above and below the knee. The drug product is administered by a trained physician in the office and is not intended for direct use by the patient. The foam remains coherent upon administration and displaces the blood in the vein. The foam is also highly echogenic, allowing for ultrasound-guided administration of the drug product. This allows for controlled treatment of the incompetent vein segment.

The foam is produced using an aqueous solution containing povidone iodine at a concentration of 1% w/v and a gas mixture consisting of oxygen/carbon dioxide (65:35) with low nitrogen content. The foam is formulated in a system designed to create consistent physical foam characteristics while allowing for rapid bubble absorption following injection into the vein. The foam transfer unit is attached to the povidone iodine canister after activation.

The product is dispensed via a sterile container system that produces foam of consistent, controlled density and bubble size (median bubble diameter < 100 micrometers (μm) and no bubbles > 500 μm) at the time of use. The product is designed to dispense sufficient foam to treat multiple patients during the course of the proposed in-use shelf life. Each canister generates 90 mL of foam. The volume of foam to be injected depends on the size and extent of the veins to be treated. The maximum recommended volume per treatment session is 15 mL, comprising individual injections up to 5 mL each. Generation of foam for each injection requires purging of (b) (4) 5 mL of foam prior to dispensing for use. After allocating for the required purge volume, each canister generates 45 mL of foam for treatment. At the end of a treatment session, the medical professional may store the drug product with the current foam transfer unit for a time not to exceed the approved in-use period. A new foam transfer unit is used for each treatment session. Each administration kit allows for up to three treatment sessions per box.

C. Basis for Approvability or Not-Approval Recommendation

We recommend a complete response action for NDA 205098. The applicant did not respond to all product quality deficiency comments communicated prior to finalizing this review. The remaining deficiencies pertain to the adequate control of drug product content uniformity through the life of the canister, across canisters, and across batches. Additional deficiency comments relate to the proposed carton and container labels. Finally, the overall facilities recommendation from the Office of Compliance is still pending at the time of review filing. Based on these factors, we recommend a complete response action at this time.

III. Administrative**A. Reviewer's Signature**

Wendy I. Wilson-Lee

Wendy I. Wilson-Lee, Ph.D.

B. Endorsement Block

WWilsonLee: 04-NOV-2013

KSrinivasachar: 06-NOV-2013

OStephens: 06-NOV-2013

C. CC Block

TBoiue

MMonteleone

30 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

WENDY I WILSON-LEE
11/07/2013

OLEN M STEPHENS
11/07/2013

NDA 205098

Polidocanol Injectable Microfoam

Provensis Ltd.

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

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Chemistry Review Data Sheet

- 1. NDA: 205098
- 2. REVIEW: 01
- 3. REVIEW DATE: 23-AUG-2013
- 4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.
- 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
None.	-

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (SD34)	02-AUG-2013
Amendment (SD 33)	24-JUL-2013
Amendment (SD 32)	24-JUL-2013
Amendment (SD 29)	09-JUL-2013
Amendment (SD 28)	05-JUL-2013
Amendment (SD 26)	14-JUN-2013
Amendment (SD 20)	16-MAY-2013
Amendment (SD 19)	16-MAY-2013
Amendment (SD 15)	01-MAY-2013
Amendment (SD 13)	23-APR-2013
Amendment (SD 11)	15-APR-2013
Amendment (SD10)	08-APR-2013
Amendment (SD 6)	11-MAR-2013
Amendment (SD 5)	05-MAR-2013
Amendment (SD 3)	28-FEB-2013
Amendment (SD 2)	13-FEB-2013
Original (SD 1)	01-FEB-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Provensis Ltd
Address:	5 Fleet Place London, UK EC4M 7RD
Representative:	<u>US Agent</u> BTG International, Inc. Five Tower Bridge Suite 800 West Conshohocken, PA 19428
Telephone:	Andreia Collier Vice President, Regulatory Affairs 215-317-0264 (p) 610-278-1605 (f)

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

- | | |
|---|----------------------|
| a) Proprietary Name: | Varithena (proposed) |
| b) Non-Proprietary Name (USAN): | Laureth 9 |
| c) Code Name/# (ONDQA only): | PEM |
| d) Chem. Type/Submission Priority (ONDQA only): | |
| • Chem. Type: | 5 |
| • Submission Priority: | S |

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

10. PHARMACOL. CATEGORY: Sclerosant

11. DOSAGE FORM: Foam

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Intravenous

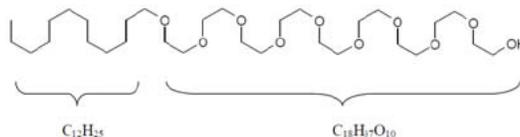
14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed Not a SPOTS product

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

Chemical Name: Polyethylene Glycol Monododecyl Ether
Mol. Formula: C₃₀H₆₂O₁₀
Mol. Weight: 582.9 (average of 9-mole adduct)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	REVIEW DATE	COMMENTS
(b) (4)	III		(b) (4)	4	N/A	-	(b) (4)
	III			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)

Executive Summary Section

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63420	Sclerosant for the treatment of moderate to severe varicose veins

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION*	DATE	REVIEWER
Biometrics	-	-	-
EES	Pending.	-	V. Shah & S. Hertz
Pharm/Tox	Pending.	-	W. Link
Biopharm	No biowaivers needed.	18-MAR-2013	B. Zolnik
LNC	Pending.	-	-
Methods Validation	Not required.	24-AUG-2013	W. Wilson-Lee
DMEPA	Pending.		K. DeFrantz
EA	Categorical exclusion granted.	24-AUG-2013	W. Wilson-Lee
Microbiology	Pending.	-	S. Langille
CDRH – Device	No concerns regarding device design or microfoam generation.	08-AUG-2013	J. Banik
CDRH – Chem. & Mat. Sci	No chemical-device interactions noted.	29-JUL-2013	M. McDermott
CDRH – Human Factors	One deficiency identified. Final recommendation pending.	23-APR-2013	Q. Nguyen

* Consults/Related Reviews listed as pending were not finalized in DARRTS at the time of primary product quality review completion.

Chemistry Review for NDA 205098

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend a complete response action for NDA 205098.

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

There are no product quality Phase 4 agreements.

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 is very soluble in methanol, ethanol, acetone diethyl ether and chloroform, and is freely soluble in water.

The regulatory drug substance specification controls [REDACTED] (b) (4)

[REDACTED]

All drug substance analytical procedures are appropriate and validated for their intended use. Based on the drug substance stability data and in accordance with ICH Q1E, we grant a [REDACTED] (b) (4) retest period for polidocanol drug substance stored at [REDACTED] (b) (4)

The drug product is a bi-canister, drug-device combination product that produces microfoam for intravenous administration once activated. One canister contains a [REDACTED] (b) (4) polidocanol solution that contains compendial excipients. The other [REDACTED] (b) (4) canister contains pressurized oxygen that is used to generate the microfoam after activation. [REDACTED] (b) (4)

[REDACTED]

Each drug product is supplied as follows:

Executive Summary Section

- A Tyvek pouch containing two sterile (b) (4) mL aluminum alloy canisters connected as a bi-canister system; one canister contains the (b) (4) povidone iodine solution; the other canister contains pressurized oxygen.
- Three microfoam transfer units used to dispense the microfoam from the canister
- Three administration boxes, each containing three, 10 mL silicone-free Luer syringes; a 20-inch manometer tube; and two compression pads.

The regulatory drug product specification for the bi-canister drug product before activation controls appearance of device (visual) and gas pressure of each pressurized canister. The regulatory drug product specification for the bi-canister drug product after activation controls appearance of microfoam (visual); visible particulates (visual); sub-visible particulates; microfoam density (b) (4); microfoam half separation time (b) (4); bubble size (b) (4); extractable volume (b) (4); identity (b) (4); pH of solution (b) (4); assay (b) (4); related substances (b) (4); sterility; endotoxin level (b) (4)

(b) (4) and content uniformity. All drug product analytical procedures, with the exception of sub-visible particulates and content uniformity, are appropriate and validated for their intended use. Based on the drug product stability data and in accordance with ICH Q1E, we grant an 18 month expiration date for 1% strength povidone iodine injectable microfoam stored at controlled room temperature in the commercial packaging. The OPS Microbiology recommendation regarding the in-use expiration period is still pending.

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

The proposed indication is the treatment of incompetent great saphenous veins, accessory saphenous veins, and visible varicosities of the great saphenous vein system above and below the knee. The drug product is administered by a trained physician in the office and is not intended for direct use by the patient. The microfoam remains coherent upon administration and displaces the blood in the vein. The microfoam is also highly echogenic, allowing for ultrasound-guided administration of the drug product. This allows for controlled treatment of the incompetent vein segment.

The microfoam is produced using an aqueous solution containing povidone iodine at a concentration of 1% w/v and a gas mixture consisting of oxygen/carbon dioxide (65:35) with low nitrogen content. The microfoam is formulated in a system designed to create consistent physical microfoam characteristics while allowing for rapid bubble absorption following injection into the vein. The microfoam transfer unit is attached to the povidone iodine canister after activation.

The product is dispensed via a sterile container system that produces microfoam of consistent, controlled density and bubble size (median bubble diameter < 100 micrometers (μm) and no bubbles > 500 μm) at the time of use. The product is designed to dispense sufficient microfoam to treat multiple patients during the course of the proposed in-use shelf life. Each canister generates 90 mL of microfoam. The volume of microfoam to be injected depends on the size and extent of the veins to be treated. The maximum recommended volume per treatment session is 15 mL, comprising individual injections up to 5 mL each. Generation of microfoam for each injection requires purging of (b) (4) 5 mL of microfoam prior to dispensing for use. After allocating for the required purge volume, each canister generates 45 mL of microfoam for treatment. At the end of a treatment session, the medical professional may store the drug product with the current microfoam transfer unit for a time not to exceed the approved in-use period. A new microfoam transfer unit is used for each treatment session. Each administration kit allows for up to three treatment sessions per box.

C. Basis for Approvability or Not-Approval Recommendation

We recommend a complete response action for NDA 205098. The applicant did not respond to all product quality deficiency comments communicated prior to finalizing this review. In addition, our primary review includes new deficiency comments to be communicated to the sponsor. The remaining deficiencies pertain to the adequate control of product quality for both the drug substance and drug product. Additional deficiency comments relate to the proposed carton and container labels. The recommendation from the microbiology review team regarding the in-use expiration period is still pending. Finally, the overall facilities recommendation from the Office of Compliance is still pending at the time of review filing. Based on these factors, we recommend a complete response action at this time.

III. Administrative**A. Reviewer's Signature**

Wendy I. Wilson-Lee

Wendy I. Wilson-Lee, Ph.D.

B. Endorsement Block

WWilsonLee:	26-AUG-2013
KSrinivasachar:	26-AUG-2013
RSood:	29-AUG-2013

C. CC Block

TBouie
MMonteleone

120 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

WENDY I WILSON-LEE
08/29/2013

RAMESH K SOOD
08/30/2013

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	205-098
Submission Date	2/4/2013
Product name, generic name of the active	Polidocanol Injectable Microfoam
Dosage form and strength	Injectable microfoam, 1%
Route of Administration	Intravenous
Applicant	Provensis Ltd. (London, United Kingdom)
Clinical Division	Division of Cardiovascular and Renal Products
Type of Submission	505 (b) (1)
Biopharmaceutics Reviewer	Banu S. Zolnik, PhD
Biopharmaceutics Secondary Reviewer	Sandra Suarez-Sharp, PhD
Biopharmaceutics Team Leader	Angelica Dorantes, PhD

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		X	The application contains 1% polidocanol drug solution in the drug product, dissolution data is not required.
2.	Is the dissolution test part of the DP specifications?		X	Refer to Comment 1
3.	Does the application contain the dissolution method development report?		X	Refer to Comment 1
4.	Is there a validation package for the analytical method and dissolution methodology?	X		Validation report for polidocanol identification will be reviewed by CMC reviewer.
5.	Does the application contain in vitro alcohol induced dose dumping studies?		X	N/A
6.	Does the application include a biowaiver request?	X		There are two biowaiver requests included in the submission as follows: <ul style="list-style-type: none"> • Biowaiver of the BE study required for bridging the two formulations tested in phase 3 clinical trials (formulation change) • Biowaiver of the BE study required for bridging to the Reference product

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

7.	Is there information provided to support the biowaiver request?			<p>The data supporting the formulation change is based on PK Study 008, which will be reviewed by OCP.</p> <p>The data provided to support the bridging to the reference drug is based on components/ composition comparisons.</p> <p>During the filing meeting with the review team, Medical Officer Dr. Khin U stated the following:</p> <p>1) The review team is not relying on any safety and efficacy data obtained from the Asclera® to support the approval of the proposed product.</p> <p>2) The review team is not relying on any safety and efficacy data obtained with the Original Formulation in support of the approval of the proposed product, which is also to be marketed formulation. Please refer to Comment 12 for further details.</p> <p>Therefore, it is concluded that the biowaiver requests are not relevant.</p>
8.	Does the application include an IVIVC model?		X	N/A
9.	Is information such as BCS classification mentioned, and supportive data provided?		X	N/A
10.	Is information on mixing the product with foods or liquids included?		X	N/A
11.	Is there any <i>in vivo</i> BA or BE information in the submission?		X	The applicant did not submit any BE data.
12.	Are there any manufacturing changes implemented to the clinical trial and bio batch formulations?	X		<p>Clinical studies were conducted using two different PEM formulations. (b) (4)</p> <p style="text-align: center;">Original formulation consisted of (b) (4)</p> <p style="text-align: center;">and the new formulation consisted of oxygen and carbon dioxide in a 65:35 ratio with low residual nitrogen. The nitrogen content is below 0.8%.</p> <p>Phase 3 clinical trials were conducted (VAP.VV017) or on going (VAP.VV015 and VAP.VV016) with the new formulation with low nitrogen levels.</p>

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

13.	Is there any data to submitted to support the manufacturing changes	X	The data supporting the formulation change is based on PK Study 008, which will be reviewed by OCP.
14.	Is there any data submitted to support the proposed dissolution specification?	X	N/A

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
15.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
16.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.		X	N/A
17.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.		X	N/A
18.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	Note that since the biowaivers included in this NDA are not relevant for the approval of the proposed product, this review concludes the Biopharmaceutics involvement in the review of this NDA.

BIOPHARMACEUTICS INITIAL ASSESSMENT

SUMMARY

The applicant, Provensis Ltd, submitted this 505 (b)(1) application for drug/device combination product of Polidocanol Injectable Microfoam for the indication of the treatment of incompetent great saphenous veins, accessory saphenous veins and visible varicosities of the great saphenous vein (GSV) system above and below the knee.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

Polidocanol Injectable Microfoam has been developed as proprietary engineered microfoam formulated from an aqueous polidocanol solution and a gas mixture consisting of oxygen/carbon dioxide (65:35) with low nitrogen content. The product is dispensed via container system that produces the microfoam. It is noted that during the drug product development, (b) (4)

In the original formulation (aka Varisolve OF), (b) (4)

The new formulation (aka low nitrogen formulation, or Varisolve NF or NF1), consists of oxygen and carbon dioxide in a 65:35 ratio with low residual nitrogen. The nitrogen content is below 0.8%. The Applicant states that both formulations of PEM were compared in Study 011 and that no differences in efficacy or safety were observed. According to the Applicant, the to be marketed formulation has been evaluated in the pivotal phase 3 clinical trial VAP.VV017 or on going trials VAP.VV015 and VAP.VV016, including clinical pharmacology study VAP.VV008 (aka Study 008).

The applicant requests a biowaiver of any BE study that may be required to bridge the formulation changes described above based on the results of the pharmacokinetic Study 008. In the PK Study 008, the Applicant evaluated the “to-be-marketed” formulation with low nitrogen levels at 1.0% and 2.0% dose strength. OCP will review the PK data.

The applicant included another request for waiver of in vivo bioavailability studies per 21 CFR 320.22 (b) (1) (i-ii) in the 1.12.15 section of the application. In this section, the biowaiver requested included a table provided below comparing the Polidocanol Injectable Microfoam formulation to the FDA approved Asclera® (NDA 21-201) drug product. (b) (4)

biowaiver request is not applicable since the applicant’s dosage form is different from Asclera®. Upon consulting with the medical officer for this application, Dr. Khin U, it was made clear that the review team is not relying on any safety and efficacy data obtained from the Asclera® to support the approval of the proposed product.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

Table 1: Polidocanol Injectable Microfoam and Asclera Ingredients

Material	Polidocanol Injectable Microfoam		Asclera (Product Label)	
	Weight in Canister (18mL)	% Composition	Weight in ampule (2mL)	% Composition
Polidocanol	(b) (4)		(b) (4)	
Ethanol (b) (4)				
Disodium Hydrogen Phosphate Dihydrate				
Potassium Dihydrogen Phosphate				
(b) (4)				

Based on the discussion during the filing meeting with the review team on 3/14/2013, Medical Officer, Dr. Khin U confirmed the following:

1. The review team is not relying on any safety and efficacy data obtained from the Asclera® to support the approval of the proposed product.
2. The review team is not relying on any safety and efficacy data obtained with the Original Formulation in support of the approval of the proposed product which is also the “to-be-marketed” formulation.

Therefore, it is concluded that the biowaiver requests are not relevant. ,.

RECOMMENDATION:

From the ONDQA-Biopharmaceutics perspective, NDA 205098 Polidocanol Injectable Microfoam is fileable.

{See appended electronic signature page}

Banu S. Zolnik, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

03/14/13
Date

{See appended electronic signature page}

Sandra Suarez Sharp, Ph.D.
Secondary Signature
Office of New Drug Quality Assessment

03/14/13
Date

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

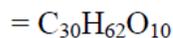
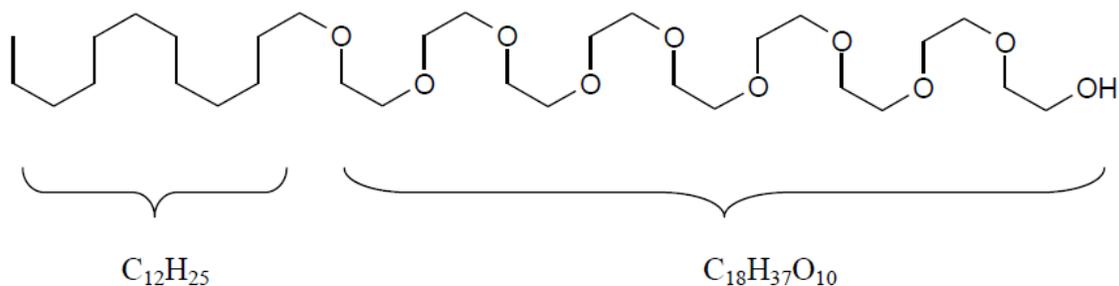
/s/

BANU S ZOLNIK
03/18/2013

SANDRA SUAREZ
03/18/2013

Initial Quality Assessment Branch I

OND Division: Division of Cardiovascular and Renal Products
NDA: 205098
Applicant: Provensis Ltd. (London, United Kingdom)
Stamp Date: 2/4/2013
PDUFA Date: 12/4/2013
Application Type: 505 (b)(1)
Drug Product Name: Polidocanol Injectable Microfoam
Trade Name: Varithena™ (pending FDA approval of name)
Code Name: Varisolve
Established Name: PEM (Polidocanol Endovenous Microfoam)
Polidocanol Endovenous Microfoam (PEM)
Polidocanol Injectable Microfoam
Dosage Form: Injectable Microfoam (new dosage form application submitted to USP)
Route of Administration: intravenous injection
Indication: Treatment of incompetent great saphenous veins, accessory saphenous veins and visible varicosities of the great saphenous vein (GSV) system above and below the knee.
Assessed by: Charles Jewell
ONDQA Fileability:



Structural Formula (9-mole adduct) (This product has a structural formula

$CH_3(CH_2)_{11}(OCH_2CH_2)_nOH$ where $n =$ an average of nine.)

Average Molecular Mass: 582.9 g/mole base on average of nine ethylene glycol moieties

USAN: Laureth 9

INN: Lauromacrogol 400

Non-Proprietary: Polidocanol

CAS #: 9002092-0 or 3055-99-0

USP: Polyoxyl lauryl Ether

Ph. Eur.: Macrogol Lauryl Ether

Chemical Name: α -dodecyl- ω -hydroxypoly(oxyethylene)

Summary

There is a previously approved NDA (Asclera: NDA 21-201) that shares the same liquid formulation of polidocanol, but it is not part of a device combination and is not listed as a microfoam, but rather as an injectable solution.

Polidocanol Injectable Microfoam has been developed as a proprietary, engineered microfoam formulated from an aqueous polidocanol solution and a gas mixture consisting of oxygen/carbon dioxide (65:35) with low nitrogen content. The product is constituted as microfoam and is generated from a device that transfers the Polidocanol Injectable Microfoam to a syringe via a Microfoam Transfer Unit (MTU). Bubbles are no greater than 500 µm. Once constituted, the microfoam in the syringe must be administered to the patient within 75 seconds. The volume of microfoam injected depends on the size and extent of the veins to be treated. The maximum recommended amount per treatment session is 15 mL, comprised of individual injections of up to 5 mL each. Additional treatment sessions may be necessary if the extent requires more than 15 mL. These treatment sessions should be separated by at least 5 days.

The product remains as a microfoam upon administration, displacing blood in the treated vein. The physical properties of the microfoam, which has a mean density of (b) (4) (b) (4) (approximate liquid: gas ratio of 1:7), allows the microfoam to empty even large veins of blood and can therefore treat them with a small total dose of active sclerosant. The gas bubbles are visible by ultrasound and can be precisely directed to the incompetent veins or branches. The product is generated by a pressurized canister device, from which the microfoam is produced and transferred to a syringe through a Microfoam Transfer Unit (MTU). The syringe is detached from the MTU and used to inject the microfoam into the vein. The system comprises a bi-canister system: with the polidocanol active pharmaceutical ingredient and carbon dioxide in one canister and oxygen in a second canister. The canisters are joined together to mix their contents at the point of use.

Two formulations were used in clinical studies. The first (referred to as Varisolve OF), produced the microfoam from a gas mixture that contained (b) (4) and was used in studies COM001, VV001, VV003, and VV005 as well as one arm in Study VV011. The new, low-nitrogen formulation (referred to as Varisolve NF or NF1 or PEM, developed in 2004) was developed for all further studies.

Sponsors of this application are Provensis Ltd and BTG International BTG, both are part of BTG International group of companies. Biocompatibles UK Ltd (one of the commercial drug product manufacturing sites) is also a BTG International group company.

Provensis and Biocompatibles procedures are part of a single global Quality Management System.

The medical device components of this product have been added to module 3 as part of sections 3.2.P.1, 3.2.P.2 and 3.2.P.7.

References two FDA 510(k) applications:

[REDACTED] (b) (4)

Drug Substance

Polidocanol drug substance is manufactured by [REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED]

The drug substance has been characterized using [REDACTED] (b) (4) to confirm structure and characterize appropriate reference materials. Analytic comparisons were made between development batches and three batches from the proposed commercial manufacturer, comparing:

- Structures by [REDACTED] (b) (4)
- Melting point characteristics by [REDACTED] (b) (4) and surface tension, viscosity, density, solubility and refractive index were compared.
- Forced degradation studies [REDACTED] (b) (4).
- Stability profile are being compared.

Polidocanol is not an NME (A version was approved in NDA 21-021 in March 2010). Polidocanol (Polyoxyl lauryl ether) is referenced in USP and Ph.Eur monographs. The USP reference is an NF monograph. It is not referenced as a drug monograph, but rather as an excipient.

The oligomeric profile shows an average mean oligomer chain length of [REDACTED] (b) (4)

Impurities are determined to be:

[REDACTED] (b) (4)

(b) (4)

Analytical methods and validations are included in the application. The applicant includes what they refer to as a comparability protocol to define the criteria to establish the analytical comparability of polidocanol active pharmaceutical ingredient (API) produced by (b) (4) with the polidocanol API produced by (b) (4) (the manufacturer used in development and clinical studies). This is not what the Agency refers to as a comparability protocol so this should be withdrawn as a comparability protocol, and the comparable nature of the analytical data between two manufacturers will be treated as a review issue.

Batch analysis for three batches from (b) (4) are included in the application.

Microbial tests and Appearance of Solid tests are included.

A universal standard for the drug substance is not available. An in-house batch is used as the standard for system suitability in several of the in-house analytical methods. Other reference standards were used to aid identification of impurities.

Drug substance is stored (b) (4)

Development batches of drug substance were shown stable for (b) (4) using long term storage conditions. Three batches of drug substance from the (b) (4) commercial process have been put on stability, slated to go 60 months for long term studies (upright); 12 months accelerated; and 12 months long term (stored inverted). Data provided in the application is proposed to support a (b) (4) retest period (3 months real time data reported).

Drug Product

Polidocanol injectable microfoam is supplied as follows:

- A Tyvek pouch containing two sterile, connected (b) (4) mL aluminum alloy canisters: one containing (b) (4) polidocanol solution under a carbon dioxide atmosphere, the second containing pressurized oxygen at approximately 5.4 bar absolute. The connector joins the two canisters and activates the product.

- Polidocanol injectable microfoam generates 90 mL of microfoam which, following purging instructions contained in the IFU (instructions for use), is sufficient to yield 45 mL of usable microfoam for injection.
- Three Microfoam Transfer Units to dispense microfoam;
- Three administration boxes each containing
 - Three 10 mL silicone-free Luer syringes;
 - A 20-inch Manometer Tube;
 - Two Compression Pads

Composition:

- The polidocanol canister contains a 1.0% w/w polidocanol solution held under an atmosphere (approx. 1.2 bar absolute) of carbon dioxide.
- The oxygen canister contains oxygen at approx. 5.4 bar absolute which is used to pressurize the polidocanol canister immediately prior to use so as to permit generation of the microfoam.

- [Redacted] (b) (4)

Details of the polidocanol solution are shown here:

Table 1: Polidocanol Solution Composition

Component	Grade/Specification	Function	Amount (mg/mL)	Amount (mg/unit)
Polidocanol	Manufacturer's Specification ¹ (Polidocanol CoA)	Active Pharmaceutical Ingredient	[Redacted]	(b) (4)
Ethanol (b) (4)	Ph. Eur./USP	[Redacted]	[Redacted]	(b) (4)
Disodium hydrogen phosphate dihydrate	Ph. Eur./USP	[Redacted]	[Redacted]	[Redacted]
Potassium dihydrogen phosphate	Ph. Eur./NF	[Redacted]	[Redacted]	[Redacted]
Hydrochloric acid ²	Ph. Eur./NF	pH adjustment	[Redacted]	(b) (4)
Sodium hydroxide ²	Ph. Eur./NF	pH adjustment	[Redacted]	(b) (4)
[Redacted] (b) (4)				

Container closure:

The integrity of the product for long term storage is maintained by the primary container closure for each canister and the primary packaging components encompassing the entire product. Once activated the primary container closure for the polidocanol canister remains intact throughout the in-use period determined of the product. (The applicant indicates that this in-use period is still under negotiation with the FDA; they propose a 7-

day in-use shelf life). Since the product can deliver up to 45 mL of injectable material, and a single dose is 15 mL maximum, the applicant proposes using the drug product on multiple patients within the in-use shelf life.

Compatibility

Throughout the use process, drug product solution can have contact with the various components of the product according to the following applicant provided tables:

Table 6: Canister Components and Materials With Potential Long Term Contact with Polidocanol Solution



(b) (4)

Table 7: Canister Components and Materials With Short Term Contact with Polidocanol Solution



(b) (4)

The (b) (4) and oxygen canister were excluded from testing as it was considered that it would be unlikely that there will be contact with polidocanol solution.

Manufacturing Process Summary (Main operations performed in a



(b) (4)

Note: In-process controls set for each step. Critical control parameters are defined for each step. All discussed in the application.

Note: This is a critical property and the product is unique, so we should make sure the method adequately covers this critical parameter. Bubbles' being too large is a severe risk to patients.

Oligomer Profile

Note: We should confirm that the proposed oligomer profile is supported by data for effectiveness. Is it bioequivalent with the previously approved version (Asclera; NDA 21-201; an injectable version of polidocanol)?

Drug Product Degradation Products

Note: (b) (4) are degradation products of the drug product. (b) (4) may be formed on storage in the polidocanol containing cylinder.

Aluminum

Note: The applicant suggests aluminum studies have shown that (b) (4) levels are low (b) (4) and do not increase over the anticipated shelf-life of the product. Therefore they propose not checking for aluminum in the release specification. This should be verified by data.

Operation of the Drug/Device System

Note: This operation is fairly complex. We should strive to understand the operation completely. Then we will understand which parts contact drug material, and then we can check to make sure leachable and extractable contaminants from the device materials have been adequately controlled for.

Stability Studies

- Applicant proposes an 18 month expiration data period for properly stored drug/device combination packaged apparatus'. (Based on statistical analysis of 12 months long term storage data of primary stability lots and 6 months data at accelerated storage data.
- Applicant proposes a 7-day in-use life, after the product has been removed from primary packaging and has been activated. This is based on physico-chemical in-use data performed under 30-day and 7-day protocols on primary and site-specific batches. There are also microbial attributes data that is proposed to support prevention of microbial ingress for a 7-day period.

Executed Batch Records

- Provided for 4 different drug substance batches (3 from proposed commercial site)
- Provided for 8 different drug product batches (3 from proposed commercial site)
- Drug substance method and validation studies (11 methods)
- Drug product method and validation studies (9 methods)

Critical Issues for Review

Drug Substance

- Does oligomer profile meet NF requirements for polidocanol?
- Is drug substance sterility adequate?
- Does the drug substance manufactured at (b)(4) meet the same analytical criteria as that produced at (b)(4) (the manufacturer for clinical material)?
- What the applicant is calling a comparability protocol is not what the Agency refers to as a comparability protocol, have the applicant correct this.

Drug Product

- Is evidence of low aluminum exposure adequate? (Drug product components stored in aluminum canisters for storage).
- Adequacy of data to support proposed 7-day in-use life of drug product after actuated.
- Is (b)(4) method adequately demonstrated?
- Are sterility methods and quality control methods adequate for this product?
- Should microbiology be consulted?
- Coordination of CDRH device review with drug substance and other drug product components? Compatibility issues?
- The applicant is requesting a biowaiver for bioavailability studies based on the polidocanol formulation being the same as that of the approved drug (Asclera; NDA 21-201; an injectable version of polidocanol). However, it is not really the same formulation since it is premixed with oxygen and carbon dioxide whereas the Asclera is injected with "regular air". Is this distinction important? It appears applicant is claiming it is not in the bioavailability sense, but it is in providing motivation for a new dosage form. For this application, systemic bioavailability is not desirable. Bioavailability is only desired in the localized vein. How likely is this product to be different than Asclera in the bioavailability sense?

Additional Issues

Administrative:

Establishment Evaluation:

Establishment Name	Responsibilities for this application
Biocompatibles UK Ltd Chapman House, Farnham Business Park Weydon Lane Farnham, Surrey, United Kingdom GU9 8QL FEI: 3002124545 DUNS: 222870839	GMP manufacture and release of the Polidocanol Injectable Microfoam (drug product), Component Testing, Labeling of canisters (Oxygen and Polidocanol) secondary packaging. Site ready for inspection.

(b) (4)



Environmental Assessment: Claim for Categorical Exclusion based upon anticipated release into the aquatic environment significantly less than 1 ppb (21 CFR 25.31 (b)).

Request for Waiver of In-Vivo Bioavailability Studies: Claim for waiver based on an approved drug (b) (4) (Asclera; NDA 21-201; an injectable version of polidocanol) (21 CFR 320.22 (b)(1)(i-ii)). This should be checked by biopharmaceutics, the previous version was not a microfoam, and no gases were present. The reason this drug is not filed as a 505 (b)(2) is since it is a novel dosage form. It seems by this waiver request, are they indicating that from the bioavailability perspective, it is not different?

Draft Carton and Container Labels:

- Instructions for Use: Consult with DMEPA and/or Human Factors in CDRH?
- One package of the bi-canister carton is labeled to supply 45 ml of usable microfoam, when 15 mL is the maximum dose per treatment. Does data support adequacy of multiple uses of the bi-canister?
- 1 % Polidocanol canister has 5 mL aliquot record, is this an adequate way to track use?
- What is adequate shelf-life for pre-foamed canisters?
- Specialized training is required for those administering this product, both with and without duplex ultrasound.
- Median bubble diameter is less than 100 microns, with no bubbles greater than 500 microns. Is this adequate?

Review, Comments and Recommendation: The drug product formulation is the same as for a previously approved drug (Asclera; NDA 21-201; an injectable version of polidocanol). This product differs in that a device is used to control the bubble size in the foam (microfoam); to prevent exposure to nitrogen; and prevent drug substance exposure to oxygen until actuation. (b) (4)

(b) (4) Drug product formulation before actuation is stored in a pressurized cylinder of carbon dioxide.

The overall system (bi-canister storage device) is (b) (4)
(b) (4) Other components to the system (including the microfoam transfer unit (MTU)) (b) (4)

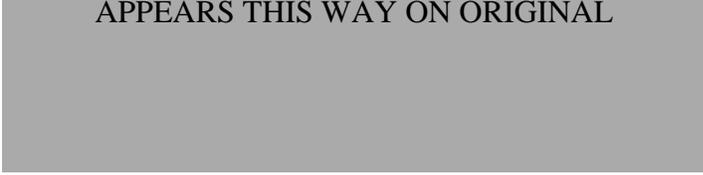
Overall, the application is adequately organized and complete, so it appears to be acceptable for filing from the CMC perspective. There are review issues highlighted above in the Critical issues for review section.

A potential 74-day letter issue is the inadequacy of the comparability protocol. It is not in the form of a comparability protocol. It should be withdrawn from the application as is.

Consults have been sent by Debbie Mesmer to OPS Microbiology and CDRH. Confirm that reviewers from Micro, CDRH and ONDQA biopharmaceutics have been assigned.

Charles Jewell, Ph.D. (CMC Reviewer)
Kasturi Srinivasachar, Ph.D. (CMC Lead)

APPEARS THIS WAY ON ORIGINAL



PRODUCT QUALITY (Small Molecule) p. 14 of 20
FILING REVIEW FOR NDA 205098 (ONDQA)

NDA Number: 205098 **Supplement Number and Type:** SDN 1 (eCTD 0000) **Established/Proper Name:** Polidocanol Injectable Microfoam

Applicant: Provensis Ltd. **Letter Date:** 2/1/2013 **Stamp Date:** 2/4/2013

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	Y		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	Y		
3.	Are all the pages in the CMC section legible?	Y		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	Y		The adequacy is a review issue

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	Y		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

PRODUCT QUALITY (Small Molecule) p. 15 of 20
FILING REVIEW FOR NDA 205098 (ONDQA)

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	Y		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	Y		

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FILING REVIEW FOR NDA 205098 (ONDQA)

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	Y		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	Y		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESSMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	Y		Assessment estimate to qualify for categorical exclusion.

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FILING REVIEW FOR NDA 205098 (ONDQA)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	Y		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	Y		
14.	Does the section contain information regarding the characterization of the DS?	Y		
15.	Does the section contain controls for the DS?	Y		
16.	Has stability data and analysis been provided for the drug substance?	Y		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		N	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		N	

PRODUCT QUALITY (Small Molecule) p. 18 of 20
FILING REVIEW FOR NDA 205098 (ONDQA)

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	Y		This is a drug/device combination product.
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	Y		
21.	Is there a batch production record and a proposed master batch record?	Y		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	Y		
23.	Have any biowaivers been requested?	Y		Because an approved drug with basically the same formulation. Adequacy is a review issue.
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	Y		
25.	Does the section contain controls of the final drug product?	Y		
26.	Has stability data and analysis been provided to support the requested expiration date?	Y		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		N	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		N	

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FILING REVIEW FOR NDA 205098 (ONDQA)

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	Y		Sponsor will send what is needed on request.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		N	Sterility and Bacterial Endotoxins are discussed in 3.2.P.5 6.2.12. and 6.2.13. Adequacy is a review issue.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	Y		see below

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	11/19/2012	
	III			11/12/2012	see (b) (4) in below DMF (b) (4)
	III			no LOA, info referenced in above DMF (b) (4)	specs. in DMF (b) (4)

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	Y		
33.	Have the immediate container and carton labels been provided?	Y		

PRODUCT QUALITY (Small Molecule) p. 20 of 20
FILING REVIEW FOR NDA 205098 (ONDQA)

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	Y		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		N	The comparability protocol is inadequate and should be withdrawn from the application. There may be other issues discovered after the date of this filing review.

{See appended electronic signature page}

Name of
 Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer
 Division of Pre-Marketing Assessment #
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Name of
 Branch Chief
 Division of Pre-Marketing Assessment #
 Office of New Drug Quality Assessment

Date

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

/s/

CHARLES F JEWELL
02/22/2013

RAMESH K SOOD
02/22/2013