

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA Number: 205098

IND Number: 63420

Submission Type: 505 (b)(1) Code:S

Applicant Name: BTG Provensis Ltd, London, UK

Submission Dates: 2-4-2013

Brand Name: Varithena®

Generic Name: Polidocanol injectable microfoam

Dosage Form: Injectable microfoam 1%

Dosage Strengths: 1% (1.3 mg polidocanol/mL microfoam)

Proposed Indication: Treatment of incompetent great saphenous veins, accessory saphenous veins and visible varicosities of the great saphenous vein system, above and below the knee accessory saphenous veins above the knee

OCP Division: DCRP

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1 EXECUTIVE SUMMARY

BTG Provensis Ltd. seeks the approval of Polidocanol Endovenous Microfoam PEM Varithena® for the treatment of incompetent great saphenous veins (GSV), accessory saphenous veins and visible varicosities of the GSV system above and below the knee. Currently 0.5% and 1% aqueous solutions of polidocanol are marketed in Europe and the US as Asclera®.

In support of the indication, the applicant conducted two adequate and well controlled Phase 3 studies (studies 0015 and 0016) with long term extensions. The two studies investigated different dose strengths including 0.125, 0.5, 1 and 2% PEM and the vehicle. The to-be-marketed formulation PEM 1% was used in both Phase 3 clinical trials. The duration of the treatments was 8 weeks in both studies.

The endpoints related to symptoms and appearance. In both studies the primary endpoint was the change from baseline in varicose vein symptoms questionnaire, assessing duration and intensity (VVSymQ with 6 and 11 point scales of the 5 most important varicose vein symptoms). The co-secondary endpoints included the change from baseline of the central Independent Photography Review-Visible Varicose Veins (IPR-V³), and the Patient Self-assessment of Appearance of Visible Varicose Veins (PA-V³) assessed by photography. The tertiary endpoint included measurement of venous reflux by duplex ultrasonography, change from baseline in the Venous Insufficiency Epidemiological and Economy Study-Quality of Life/Symptoms score assessed by the patient (VEINES QOL), and change from baseline in the Venous Clinical Severity Score assessed by the physician (VCSS).

The Clinical Pharmacology part of the submission contains 3 studies with PK information: Study 08 is the pivotal PK study that used to be marketed formulations of PEM and assayed the plasma concentrations of 4 polidocanol oligomers using a sensitive enough assay method. The possible impact of polidocanol on QTc and the other ECG intervals was also investigated in this study. Studies 005 and 011 represent pilot PK studies. In addition to the 3 reports of *in vivo* studies in humans, there were 7 reports of *in vitro* studies, 3 on the metabolism, 1 on the plasma protein binding and red blood cell partitioning, 1 on the absorption of the gaseous constituents of the microfoam in whole blood, 1 on the hemolytic effects of polidocanol and 1 examining the possibility that high concentrations of polidocanol remain in the venous system after intravenous injection of PEM. In addition, there was a mass balance study in dogs with information useful for the interpretation of the PK findings in man.

The reviewed studies included the pivotal PK study 008, the 7 *in vitro* studies and the mass balance study in dogs. Study 005 in humans was not reviewed because it used a

preliminary formulation of PEM and the assay applied was less sensitive than the assay used in Study 008. Study 011 was not reviewed because of the insufficient sensitivity of the assay method used that limited the follow-up of the plasma concentration profiles of the polidocanol oligomers to 60 min after injection, a time interval too short to determine reliably PK parameters for the 4 oligomers of polidocanol.

1.1 Recommendations

From a Clinical Pharmacology viewpoint the submitted clinical pharmacology package supports approval of NDA105098.

1.2 Phase 4 Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The key findings are listed below:

Pharmacokinetics

- The selected 4 oligomers of polidocanol, E5, E9, E12 and E14 tend to exhibit a less than dose proportional pharmacokinetics in males and females. The respective apparent terminal $t_{1/2}$ of the oligomers range between 1 and 2.5 h. The respective dominant half-lives of the oligomers are shorter
- Plasma protein binding of polidocanol is saturable
- The predominant route of elimination of the selected oligomers is metabolism.
- Body weight, but not sex is a covariate for the pharmacokinetics of the oligomers

Safety

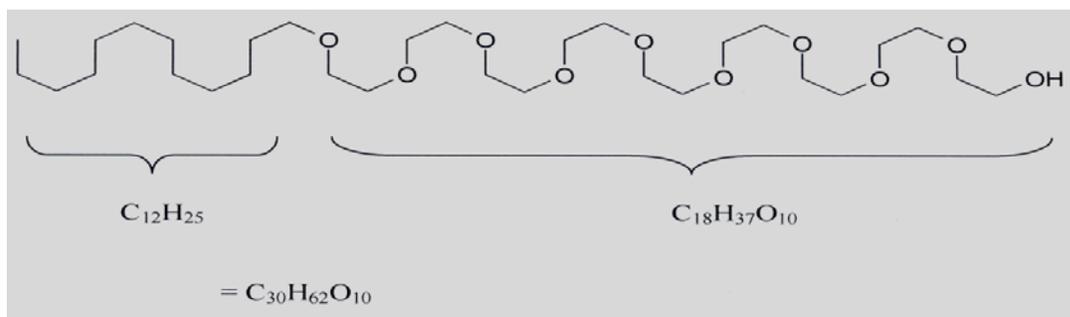
- Polidocanol does not significantly prolong the QTcF interval

2 QUESTION BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

The drug substance polidocanol (hydroxypolyethoxydodecane) consists (b) (4) of ethylene glycol units with the molecular formula $C_{12}H_{25}(OCH_2CH_2)_xOH$, where x has an average value of 9 as shown in the below figure:



The molecular weight of polidocanol is (b) (4)

The drug formulation, polidocanol endovenous microfoam (PEM) is produced by mixing an aqueous polidocanol solution and an O₂:CO₂ (65:35) gas mixture with a trace of N₂. PEM is produced using a sterile bi-canister system designed to create a microfoam with stable physical characteristics, consistent density and bubble size (median diameter < 100 μm and no bubble greater than 500 μm) at the time of use.

In vitro safety studies have shown that polidocanol microfoam does not induce hemolysis at therapeutic concentrations of polidocanol. The polidocanol concentrations in close proximity of the microfoam bubbles are not increased. The absorption of the gas bubbles is rapid: 50% of the gas is absorbed in 6 sec. No bubbles were detectable in the right heart chamber after administration of the final formulation of polidocanol microfoam. Previous formulations containing up to (b) (4) N₂ produced bubbles that were detectable in the heart by echocardiography.

The microfoam generating system is depicted in the below figure:

PEM remains intact upon administration and displaces the blood in the vein. By emptying the vein from blood PEM impacts the endothelium of the vessel directly. PEM is also echogenic and can be observed filling the intended segments of incompetent veins.

PEM is dispensed from a proprietary canister device which generates sufficient microfoam to treat several patients during its in use shelf life. The Microfoam Transfer Unit, a component of the device used to dispense PEM to a syringe for injection into the target veins, must be replaced between patients.

The composition of the polidocanol solution is shown below:

Table 2: Polidocanol Solution 1.0% (b) (4) Specifications

Material	Quantities
	% w/w
Polidocanol	1.0% (b) (4)
Ethanol (b) (4)	4.200
Disodium hydrogen phosphate dihydrate EP/NF	0.240
Potassium dihydrogen phosphate, EP/NF	0.085
0.1M Sodium hydroxide solution	q.s.
0.1M Hydrochloric acid solution	q.s.
	(b) (4)
TOTAL	100.00%

% w/w = weight/weight
 EP/NF = European Pharmacopeia / National Formulary
 qs = sufficient quantity
 EP/USP = European Pharmacopeia / United States Pharmacopeia

2.1.2 What are the proposed mechanism of action and therapeutic indications?

The oligomers contained in polidocanol exhibit sclerosant, detergent and local anesthetic activities. Injection into a vein results in endothelial sclerosis and thrombus formation. Polidocanol is indicated for the treatment of incompetent great saphenous veins, accessory saphenous veins and visible varicosities of the great saphenous veins (GSV) system above and below the knee.

2.1.3 What are the proposed dosages and routes of administration?

PEM 1% is injected intravenously into an affected vein. The volume of PEM to be administered depends on the size and extent of the varicose veins. The proposed strength of PEM is 1% and the maximum volume is up to 15 mL per treatment session. Individual injections of polidocanol should not exceed 5 mL. Further treatments may be necessary if the extent of the varicose veins requires more than 15 mL PEM 1%. Treatment sessions should be separated by a minimum of 5 days. A new sterile Microfoam Transfer Unit must be used for each treatment session.

2.2 General Clinical Pharmacology

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

2 randomized, blinded, placebo controlled, multi-center Phase 3 trials of 8 week duration using the to-be-marketed formulation of PEM 0.5%, 1.0% and 2.0 % (Study 016) and 0.5% and 1.0% versus placebo or 0.125% PEM (Study 015) provided evidence for the efficacy and safety of polidocanol. A total of 519 patients were enrolled in the 2 studies. A third study with a randomized blinded design with the final formulation of PEM (Study 017) investigating efficacy and safety of 0.125%, 0.5%, 1.0% and 2.0% PEM versus placebo provided supportive evidence.

Information on the clinical pharmacology of polidocanol *in vivo* was limited to the evaluation of the pharmacokinetics of the oligomers E5, E9, E12 and E14 which was investigated in an open-label single-center study (008). Twenty-one (21) patients were randomly assigned to treatments with PEM 1% or 2%. All patients enrolled presented with varicose veins suitable for PEM treatment. Polidocanol was administered by 2 sequential injections of 5 mL separated by an interval of 10 min.

2.2.2 *What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?*

The clinical endpoints include symptoms and appearance of the injected veins. The primary endpoint in both pivotal studies (015,016) was improvement in patient symptoms, as measured by a change from baseline to Week 8 in the 7 day average electronic daily diary VVSymQ score. The VVSymQ score is a patient reported outcome measure based on daily patient assessment varicose vein symptom determined to be most important to patients: Heaviness, achiness, swelling, throbbing, and itching. The VVSymQ score ranges from 0-25, where 0 represents no symptoms and 25 represents all 5 patient's symptoms experienced all of the time.

The co-secondary endpoints in both studies was the improvement in appearance of visible varicosities from baseline to the end of week 8 as measured by: a) patients scoring the appearance of their varicose veins in the medial view of their study leg (PA-V³ score) from "Not at all noticeable" (=score 0) to "Extremely noticeable" (=score 4) and b) from an independent photography review panel rating the severity of the patient's varicose vein appearance in standardized digital photographs of the medial view of each patient's study leg (IPR-V³) with scores from "None" (=score 0) to "Very severe" (=score 4). The open-label PK study 018 of polidocanol was not designed to evaluate the exposure-response relationship.

Tertiary endpoints in the 2 pivotal studies included response to treatment as determined by a change from baseline in Venous Clinical Severity Score (VCSS) by duplex

ultrasound, and by change from baseline in Venous Insufficiency Epidemiologic and Economic Study-Quality of Life/Symptoms (VEINES-QOL) score.

2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

In the PK study 008 the sponsor measured the PK of 4 of the most abundant oligomers i.e. E5, E9, E12, and E14. (b) (4)

The plasma concentration time profiles of E5, E9, E12 and E14 were followed for 6 h.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

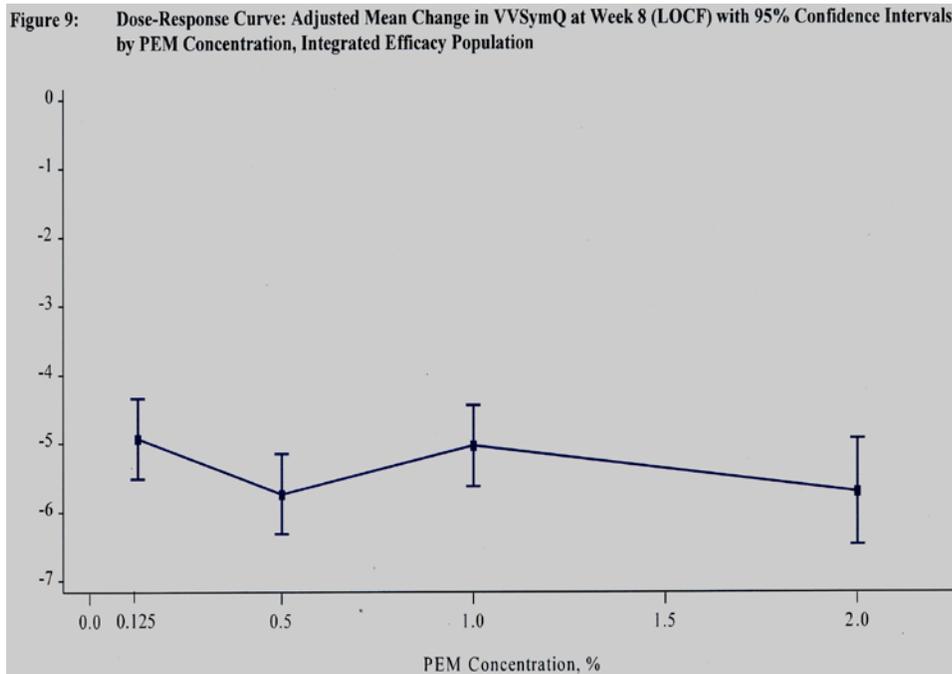
The sponsor tested a wide range of doses of polidocanol ranging between (b) (4)
mg as shown in the below table:

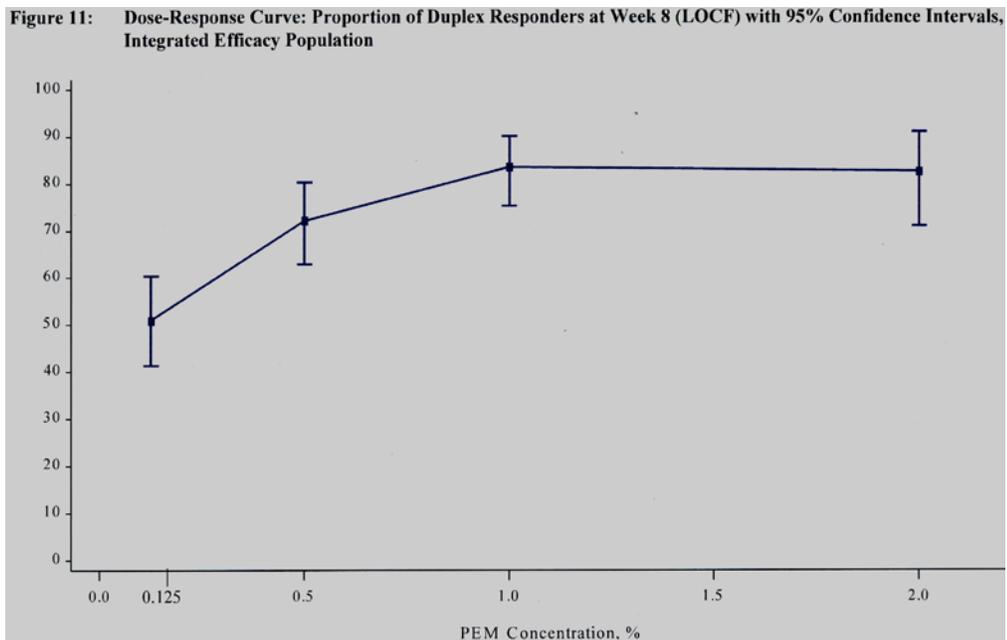
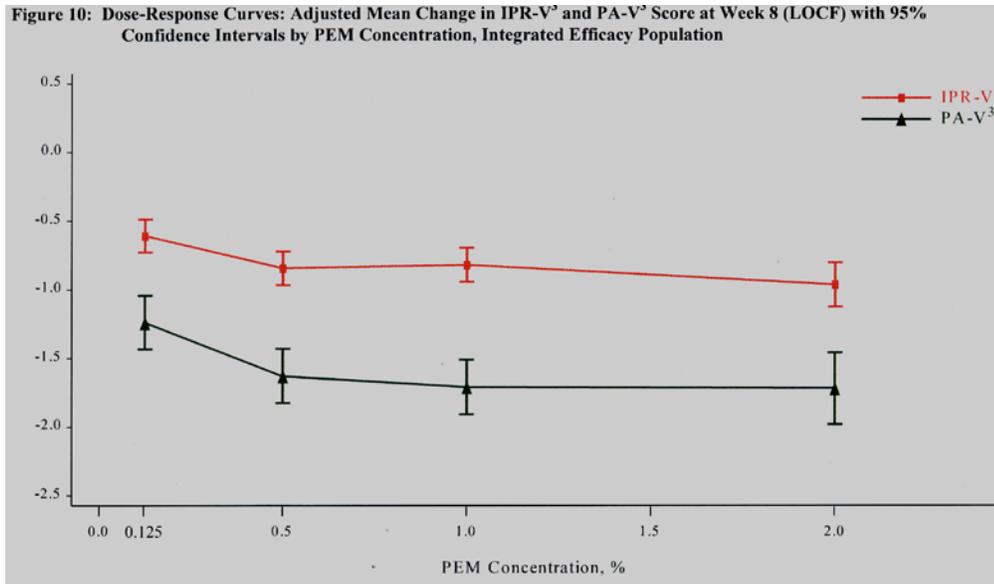
(b) (4)



Efficacy was assessed as the difference from baseline on week 8 after injection of vehicle and 0.125, 0.5, 1.0 and 2.0% PEM in study 015 and vehicle, 0.125, 0.5 and 1% in study 016. The 0.125% strength served also as a control when the efficacy of the higher strength formulations was tested with duplex ultrasound. The pivotal studies 015 and 016 were not powered to determine the difference in efficacy between the individual doses

tested. The statistical evaluation of the combined data from studies 015 and 016 shows for IPR-V³ and PA-PV³ that the efficacy of each 0.5, 1.0 or 2.0% PEM is significantly greater than for 0.125% PEM or the vehicle. A statistically significant linear trend for response across the PEM concentrations from 0.125% to 2.0% for the response in appearance endpoints of IPR-V³ and PA-V³ was shown. The efficacy of PEM 2% with VVSympQ is also statistically significantly greater than that of PEM 0.125%. Plots of the respective dose-efficacy relationships for the 3 endpoints VVSymQ (1), IPR-V³ and PA-V³ (2) and Duplex Ultrasound (3) measured in the pivotal studies 015 and 016 are shown below:





The plots indicate a flat dose-efficacy relationship for the endpoints VVSymQ and IPR-V³ and PA-V³ for the doses of 0.5, 1.0 and 2.0% PEM. More patients responded after receiving 1 or 2% PEM than 0.5% PEM with the endpoint duplex ultrasound. The 2% PEM appears not to be more efficacious than 1% PEM.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

The below table lists the percentage of patients presenting with venous thrombus events in the pivotal studies:

Vein	Treatment Group, n (All patients)					
	PEM 0.125% ^c N=130	PEM 0.5% ^d N=150	PEM 1.0% ^e N=837	PEM 2.0% ^f N=75	Pooled PEM 1.0% ^a N=1170	Pooled PEM ^b (N=1333)
Number of Patients with Venous Thrombus ^g	6 (4.6)	9 (6.0)	49 (5.9)	8 (10.7)	71 (6.1)	94 (7.1)
Number of Patients with Pulmonary Embolism ^g	0	0	0	0	0	0
Primary Location of Thrombus per Number of Patients in the Treatment Group ^g						
Common femoral vein thrombus extension	3 (2.3)	5 (3.3)	24 (2.9)	4 (5.3)	27 (2.3)	39 (2.9)
Proximal deep vein thrombosis						
Femoral vein	0	1 (0.7)	6 (0.7)	2 (2.7)	13 (1.1)	16 (1.2)
Popliteal vein	0	0	4 (0.5)	1 (1.3)	5 (0.4)	6 (0.5)
Distal deep vein thrombosis						
Posterior tibial vein	0	2 (1.3)	2 (0.2)	1 (1.3)	9 (0.8)	12 (0.9)
Anterior tibial vein	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)
Peroneal vein	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)
Isolated gastrocnemius and soleal vein thrombosis						
Soleus vein	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)
Gastrocnemius vein	3 (2.3)	1 (0.7)	10 (1.2)	0	14 (1.2)	18 (1.4)

The frequency of venous thrombus AEs was lower in patients with PEM 1% than in the group receiving PEM 2.0%. Of note the number of patients treated with PEM 1% was much larger than that treated with PEM 0.5% and 2%.

In conclusion, the results indicate no overt dose dependency of the tolerability/safety of polidocanol. Therefore, the recommended dose range of polidocanol is determined primarily by efficacy considerations. The 2% strength is not more efficacious than the 1% strength and is associated with a numerically increased number of thrombus formations with extension into the femoral vein. Therefore, the 2% strength is not preferable compared to the 1% strength. The 1% strength is not significantly superior to the 0.5% strength. The number of treatment failures is numerically greater with the 0.5% strength than with the 1% strength. Thus the 1.0 and 0.5% strength of PEM may be recommended for the label. However, the sponsor is currently only manufacturing the 1% strength. The sponsor proposes the 1% strength for marketing.

2.2.4.3 Does this drug prolong QT/QTc Interval?

A thorough QTc study was not performed with polidocanol. However, the PK study 008 investigating the effect of intravenous injections of 10 mL PEM 1% and 2% found no clinically significant prolongations of QTcF or significant quantitative changes in the RR-, PR-, and QRS-intervals or morphological ECG changes in the 21 patients investigated. The QTcF interval duration was significantly correlated with the plasma concentrations of each of the 4 oligomers E5, E9, E12 or E14.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?

Yes. See Section 2.2.4.1

2.2.5 What are the PK characteristics of the drug?

The individual PK of the 4 oligomers tend to be less than dose proportional in that the plasma concentrations after injection of 1% PEM tend to be greater than after 2% PEM which may be caused by saturable plasma protein binding.

2.2.5.1 What are the single and multiple dose PK parameters?

PEM is to be administered as a single dose injection. Therefore, pharmacokinetic information is only available after injection of a single dose or up to 3 injections injected within a 20 min interval.

The mean clearance and terminal t1/2z of E5, E9, E12 and E14 oligomers after injection of 10 mL PEM 1% and 2 % in male and female patients are listed in the below tables:

Arithmetic Mean PK Parameters for the Individual Oligomers after Injection of 10 mL PEM 1% in 6 Females and 3 Males

	Sex	Mean (CV, %)				Polidocanol
		E5	E9	E12	E14	
CL, mL/min	M	641 (26)	273 (45)	262 (31)	271 (16)	288 (33)
	F	511 (27)	203 (35)	215 (36)	260 (32)	236 (33)
t1/2, min	M	68 (17)	81 (24)	99 (10)	90 (23)	102 (10)
	F	127 (85)	80 (21)	101 (62)	58 (35)	106 (20)
Ae(0-8 h), % Dose	M	*	*	*	*	NA
	F	*	*	*	0.097 (94)	NA

* < LLOQ NA= not applicable

Arithmetic Mean PK Parameters for the Individual Oligomers after Injection of 10 mL PEM 2% in 5 Females and 6 Males

	Sex	Mean (CV, %)				Polidocanol
		E5	E9	E12	E14	
CL, mL/min	M	773 (61)	320 (40)	340 (37)	420 (58)	351 (33)
	F	575 (21)	256 (26)	274 (30)	303 (29)	291 (25)
t1/2 min	M	117 (39)	122 (31)	139 (34)	122 (79)	153 (38)
	F	79 (32)	68 (6.5)	87 (16)	59 (33)	114 (40)
Ae (0-8 h) % Dose	M	*	*	*	0.039 (105)	NA
	F	*	*	*	0.064 (52)	NA

* < LLOQ NA=not applicable

The CL for E5 is significantly greater than for E9, E12 and E14. The apparent t1/2z is similar among the 4 oligomers and does not change with dose. The amounts of the oligomers E5, E9 and E12 recovered in urine are too small to be measurable by the LC-MS/MS method used. The percentage of the dose recovered as unchanged E14 in urine is ≤ 0.23% indicating that the oligomers are eliminated mainly by the non-renal route.

The mean values of the dose and body weight normalized peak concentrations and AUC0-tlast.com for the 4 oligomers in the male and female patients are listed in the below table:

	Dose	Sex	Mean (CV, %)			
			E5	E9	E12	E14
C _{max}	1%	M	31 (34)	41 (28)	51 (18)	63 (20)
		F	39 (57)	58 (57)	77 (50)	90 (44)
	2%	M	32 (32)	42 (31)	51 (28)	62 (30)
		F	30 (32)	41 (30)	52 (28)	64 (26)
C _{max,1}	1%	M	57 (32)	69 (35)	89 (24)	96 (16)
		F	64 (55)	82 (54)	117 (46)	130 (39)
	2%	M	47 (47)	58 (40)	73 (32)	92 (30)
		F	44 (48)	52 (44)	72 (32)	89 (18)
C _{max,2}	1%	M	30 (35)	41 (28)	51 (18)	60 (28)
		F	36 (67)	56 (60)	73 (29)	86 (49)
	2%	M	31 (31)	42 (32)	51 (29)	61 (31)
		F	30 (32)	41 (30)	52 (28)	64 (26)
AUC _{0-tlast,com} *	1%	M	1454 (18)	4587 (44)	4219 (31)	2917 (22)
		F	1350 (21)	4895 (32)	4518 (30)	3294 (21)
	2%	M	1320 (44)	3772 (39)	3369 (36)	2535 (35)
		F	1176 (20)	3343 (19)	3054 (21)	2480 (21)

*AUC₀₋₁₂₀ for E5 and E14 AUC₀₋₂₄₀ for E9 and E14

The dose and body weight normalized exposure parameters are similar in males and females indicating that body weight, but not sex, is a covariate for the PK of the polidocanol oligomers. The PK of the measured polidocanol oligomers E5, E9, E12 and E14 tend to be less than dose proportional (See also Section 2.2.5.5).

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

PK data were obtained in patients with incompetency or varicosity of the great saphenous veins. The subjects can be considered otherwise healthy. Therefore no difference in the PK of the polidocanol oligomers in most of the patients with incompetent or varicose veins and matched healthy volunteers is anticipated.

2.2.5.3 What are the characteristics of drug absorption?

Polidocanol is administered via the intravenous route

2.2.5.4 What are the characteristics of drug distribution?

The plasma protein binding of ¹⁴C-polidocanol concentration dependently decreases from 46% to 2% when the concentration is increased from 0.1 to 100 µg/mL. The plasma protein binding of ¹⁴C polidocanol was not measured at the expected peak concentration of 1.5µg/mL. Thus, the % protein binding of polidocanol in the therapeutic range remains unknown. The plasma to blood concentration ratio decreases from 1.80 at 0.01 µg/mL to 1.70 at 100 µg/mL, in agreement with saturable plasma protein binding. ¹⁴C polidocanol shows little affinity for red blood cells.

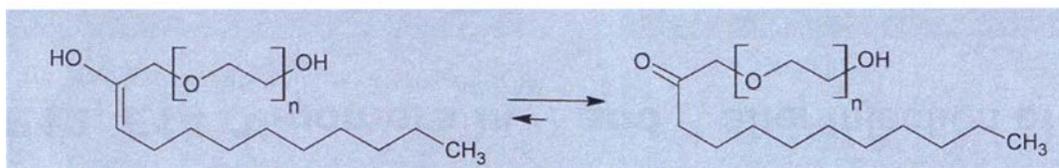
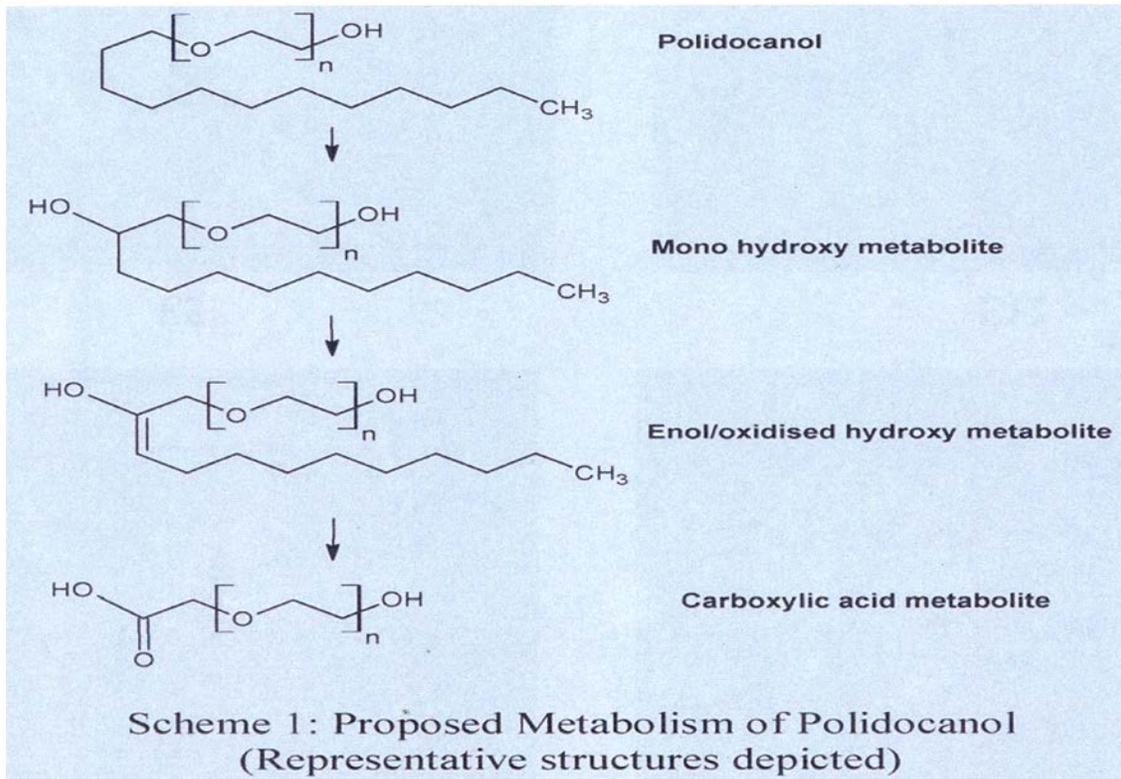
2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass balance study was not performed in humans limiting the interpretation of the pharmacokinetics of polidocanol. The percentage of the dose excreted as unchanged oligomers E5, E9, and E12 is below the LLOQ and the recovery of unchanged E14 in urine ranges been 0 and 0.097% in humans suggesting little excretion of the 4 oligomers in urine.

However, mass balance information is available from a study in 4 male dogs receiving 20.5 mg ¹⁴C-polidocanol intravenously. The findings from that study show a disposition half-life of about 1.5-2.0 h for total radioactivity representing polidocanol oligomers and possibly generated metabolites in the dog during the 0-6 h post injection interval. This value is not much greater than the estimated dominant half-life of the oligomers of 0.5 - 1.0 h in man. Additionally, the results from the study in dogs show that the mean combined recovery of total radioactivity in feces and urine 6, 24 and 168 h after injection is 47, 78 and 88%, respectively, indicating that 6 h after injection more than 50% of the dose is recovered, mainly in urine. In the 6-168 h interval the elimination of total radioactivity in urine and feces proceeds at a significantly slower pace. The dog data indicate that the polidocanol oligomers are mainly eliminated by metabolism with subsequent excretion into urine and bile. The results of the mass balance study in dogs indicate further that the polidocanol oligomers during the 0-6 h interval after injection undergo elimination not just distribution into tissues.

2.2.5.6 What are the characteristics of drug metabolism?

The extent of the metabolism of polidocanol and the oligomers E5, E9, E12 and E14 is not known in man. In vitro experiments with liver microsomes indicate that the oligomers contained in polidocanol are oxidized in the dodecyl side chain. The metabolic scheme for the metabolism is shown below:



2.2.5.7 What are the characteristics of drug elimination?

See sections 2.2.5.5 and 2.5.5.6

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

The PK of the E5, E9, E12 and E14 oligomers of polidocanol tend to be less than dose proportional when comparing the exposure after injection of 1% PEM and 2% PEM.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Polidocanol is not chronically dosed.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients?

The inter-subject variability (percent coefficient of variation about mean) for C_{max} and AUC ranges between 20-60%

2.3 Intrinsic Factors

2.3.1 *What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?*

An increase in body weight decreases the systemic exposure to polidocanol. Sex does not impact the exposure to polidocanol. The possible effect of age and race on the exposure to polidocanol is unknown.

2.3.2 *Based upon what is known about E-R relationships and their variability, what dosage regimen adjustments are recommended for each group?*

No dose adjustment is recommended for subjects based on body weight, sex, race, renal or hepatic impairment.

2.3.2.1 *Elderly*

The impact of age on the exposure to polidocanol is unknown. No dose adjustment is recommended based on age.

2.3.2.2 *Pediatric Patients*

The PK of polidocanol in children was not investigated.

2.3.2.3 *Race*

See Section 2.3.1

2.3.2.4 *Renal Impairment*

The impact of renal impairment on the exposure to polidocanol has not been determined. No dose adjustment is recommended for patients with renal impairment

2.3.2.5 *Hepatic Impairment*

The impact of hepatic impairment on the exposure to polidocanol has not been determined. No dose adjustment is recommended for polidocanol in patients with hepatic impairment.

2.3.3 *What pregnancy and lactation use information is there in the label?*

There is no use information for patients who are pregnant or lactating.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The impact of extrinsic factors such as co-administered other drugs has not been investigated with polidocanol. Because polidocanol is not administered in a multiple dose regimen the impact of other drugs on polidocanol is not expected to be significant.

2.4.2 What are the drug-drug interactions?

No *in vivo* or *in vitro* drug interaction studies were performed with polidocanol.

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

The enzymes responsible for the metabolism of polidocanol have not been identified.

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

See Section 2.4.2.1. The impact of a possible enzyme polymorphism on the metabolism in man has not been investigated.

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

The possible inhibition of CYP enzymes by polidocanol or the induction of CYP enzymes by polidocanol has not been investigated

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

The possible role of polidocanol as a substrate of P-gp and other transporters was not investigated by the sponsor. The inhibition of P-gp and other transporters by polidocanol or the possible induction of P-gp and other transporters by polidocanol has not been investigated either.

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

See Section 2.4.2.1 and 2.4.2.4

2.4.2.6 Does the label specify co-administration of another drug?

No

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

The patients who are undergoing treatment with polidocanol are usually in good health. The likelihood of significant co-medications is small.

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

No drug interaction studies have been performed with polidocanol

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

No

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

The activity of the metabolites of the oligomers contained in polidocanol in humans was not investigated. Metabolic drug interaction studies with polidocanol were not performed.

The relevance of the saturable plasma protein binding for the *in vivo* PK of polidocanol is unclear because the investigations performed at the higher concentration levels were beyond the therapeutic range. However, given that polidocanol is not administered chronically this is not a critical issue.

2.5 General Biopharmaceutics

Not applicable

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma?

The 4 oligomers, E5, E9, E12 and E14, were measured by LC-MS/MS. Potential active metabolites of the 4 oligomers have not been identified and were not measured.

2.6.2 Which metabolites have been selected for analysis and why?

No metabolites were selected for analysis.

2.6.3 For all moieties measured, is free, bound, or total measured?

In the *in vitro* plasma protein binding- and RBC partitioning-study total (bound + unbound) and unbound ¹⁴C- polidocanol was measured as total radioactivity. In the *in vivo* PK study VAP.VV008 the total (bound+ unbound) concentrations of the 4 oligomers, E5, E9, E12 and E14 in plasma and urine were measured and total polidocanol concentrations estimated from $\sum(E5+E9+E12+E14) \bullet (100/26.49)$, where 26.49 is the percentage each oligomer contributes to the total dose of polidocanol.

2.6.4 What bioanalytical methods are used to assess concentrations?

A LC-MS/MS method was used to measure the E5, E9, E12 and E14 oligomers of polidocanol in plasma and urine.

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What is curve fitting technique?

E5: Plasma: 3.1 -624 ng/mL Urine: 60-4000 ng/mL

E9: Plasma: 4.5-9.1 ng/mL Urine: 60-4000 ng/mL

E12: Plasma: 3.7-736 ng/mL Urine: 60-4000 ng/mL

E14: Plasma: 2.6-510 ng/mL Urine: 60-4000 ng/mL

The LLOQ and ULOQ are adequate for measuring the oligomers of polidocanol in the therapeutic range. The sensitivity of the assay was not sufficient for measuring the amounts of the oligomers excreted unchanged in urine.

The peak areas of E5, E9, E12 and E14 were plotted against the respective concentrations for each calibration standard. A $1/x^2$ weighted linear regression model was used to fit the data in plasma and urine.

2.6.4.2 What are the lower and upper limits of quantitation?

See Section 2.6.4.1

2.6.4.3 What are the accuracy, precision, and selectivity at these limits

Estimates for the precision and accuracy of the LC-MS/MS method for the oligomers E5, E9, E12 and E14 using QC samples analyzed along with plasma and urine samples with unknown oligomer concentrations are shown below:

Analyte		E5	E9	E12	E14
Method		LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
Matrix		Plasma	Plasma	Plasma	Plasma
Range, ng/mL		3.1-624	4.5-908	3.7-736	2.6-510
Quality Control	% CV	≤ 6.4	≤ 17	≤ 12	≤ 17
	% RE	-9.8-6.3	-3.7-5.5	-17.9-8.1	-1.2-3.7

Analyte		E5	E9	E12	E14
Method		LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
Matrix		Urine	Urine	Urine	Urine
Range, ng/mL		60-4000	60-4000	60-4000	60-4000

Quality Control	% CV	≤ 11	≤ 7.4	≤ 9.2	≤ 9.7
	% RE	-3.8-6.2	-6.0-12.2	-3.5-9.3	-2.3-7.0

The selectivity of the LC-MS/MS method for measuring the individual oligomers appears to be adequate.

2.6.4.4 What is the sample stability under conditions used in the study?

The samples were analyzed by the analytical laboratory within the stability window.

2.6.4.5 What is the QC sample plan?

See Section 2.6.4.3

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/s/

RAJANIKANTH MADABUSHI

10/30/2013

(On behalf of Dr. Peter Hinderling, the primary clinical pharmacology reviewer for this submission)

Office of Clinical Pharmacology

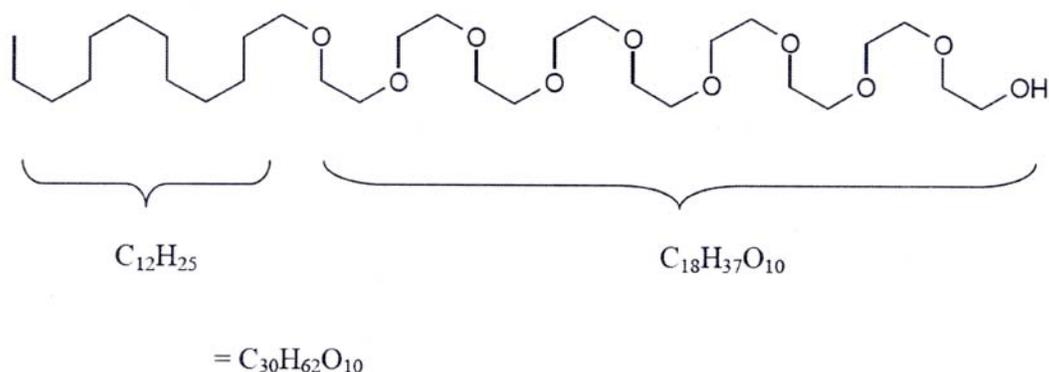
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	205098	Brand Name	Varithena®
OCP Division (I, II, III, IV, V)	I	Generic Name	Polidocanol Endovenous Microfoam
Medical Division	DCRP	Drug Class	Sclerosant
OCP Reviewer	Peter H. Hinderling, MD	Indication(s)	Treatment of incompetent great saphenous veins, accessory saphenous veins and visible varicosities of the great saphenous vein system above and below the knee
OCP Team Leader	Raj Madabushi, PhD	Dosage Form	Intravenous injection
Pharmacometrics Reviewer	—	Dosing Regimen	The volume of Varithena® injected depends on the size and extent of the varicose veins. The maximum recommended volume per treatment is 15 mL. Individual injections should not exceed 5 mL. Further treatments may be necessary if the extent of the varicose veins requires more than 15 mL of Varithena®. Treatment sessions should be separated by a minimum of 5 days.
Date of Submission	February 1, 2013	Route of Administration	Intravenous
Estimated Due Date of OCP Review	August 31, 2013	Sponsor	Provensis Ltd. London, UK
Medical Division Due Date	September 30, 2013	Priority Classification	Standard
PDUFA Due Date	December 6, 2013		

Summary

A polidocanol for the treatment of spider veins is on the market. Polidocanol is a hydrophilic polymer with the structure formula:



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: 582.0 g/mole based on average of nine ethylene oxide units.

The most abundant oligomers of polidocanol are E4, E9, E 12 and E14 which together represent about 27% of total polidocanol.

The Clinical Pharmacology part of the submission contains information on the:

- PK of polidocanol in the target population after administration of the to be marketed formulation determined in a clinical study
- Assay report of the study
- Validation report of the method
- Assay and PK information obtained in a previous clinical study

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?		X		No drug interactions are known. Metabolism of the hydrophilic polidocanol isomers is unlikely
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized,	X			

	indexed and paginated in a manner to allow substantive review to begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	Target population is healthy
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	Adequate PK information
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION
FILEABLE? _Yes_____**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

In the submission the sponsor provided PK data referenced to total polidocanol, i.e. $\Sigma E4 + E9 + E12 + E14$. The sponsor was asked to provide the plasma concentration time curves and PK parameters of the individual oligomers. The sponsor has submitted the requested additional data.

Peter H. Hinderling, MD	3-15-13
Reviewing Clinical Pharmacologist	Date
Raj Madabushi, PhD	3-15-13
Team Leader/Supervisor	Date

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

/s/

PETER HINDERLING

03/15/2013

RAJANIKANTH MADABUSHI

03/15/2013

The lack of metabolism and DDI information in this submission is not a Refuse-to-File issue because the the expected systemic availability is low and there is no expectation of significant metabolism or DDI impact.