

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205098Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 205098	
		NAME OF APPLICANT/NDA HOLDER Provensis Ltd	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) VARITHENA			
ACTIVE INGREDIENT(S) injectable microfoam of carbon dioxide and oxygen gas and aqueous polidocanol solution		STRENGTH(S) 1% polidocanol solution in 35:65 carbon dioxide:oxygen gas mixture as a microfoam with liquid to gas ratio of 1:7 to provide 1.3 mg of polidocanol per mL of microfoam.	
DOSAGE FORM injectable microfoam			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number RE38,919		b. Issue Date of Patent 12/13/2005	c. Expiration Date of Patent 10/14/2014
d. Name of Patent Owner BTG International Limited		Address (of Patent Owner) 5 Fleet Place City/State LONDON, EC4M 7RD ZIP Code UK Telephone Number +44 20 7575 0000	
		FAX Number (if available) + 44 20 7571 8799	E-Mail Address (if available) intellectual.property@btgpic.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Anthony Tridico FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER		Address (of agent or representative named in 1.e.) 901 New York Avenue, NW City/State WASHINGTON, DC ZIP Code 20001-4413 Telephone Number 202.408.4000	
		FAX Number (if available) 202.408.4400	E-Mail Address (if available) anthony.tridico@finnegan.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes
---	------------------------------

6. Declaration Certification	
<p>6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed</p> <p>12/20/2012</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name</p> <p>Anthony Patrick Dolan</p>	
<p>Address</p> <p>BTG International Ltd, 5 Fleet Place</p>	<p>City/State</p> <p>London EC4M 7RD</p>
<p>ZIP Code</p> <p>UK</p>	<p>Telephone Number</p> <p>+44 20 7575 0000</p>
<p>FAX Number (if available)</p> <p>+ 44 20 7571 8799</p>	<p>E-Mail Address (if available)</p> <p>Tony.Dolan@btgplc.com</p>
<p>The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer 1350 Piccard Drive, Room 400 Rockville, MD 20850</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

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		NAME OF APPLICANT/NDA HOLDER Provensis Ltd	
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ACTIVE INGREDIENT(S) injectable microfoam of carbon dioxide and oxygen gas and aqueous polidocanol solution		STRENGTH(S) 1% polidocanol solution in 35:65 carbon dioxide:oxygen gas mixture as a microfoam with liquid to gas ratio of 1:7 to provide 1.3 mg of polidocanol per mL of microfoam.	
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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number RE40,640		b. Issue Date of Patent 02/17/2009	c. Expiration Date of Patent 10/14/2014
d. Name of Patent Owner BTG International Limited		Address (of Patent Owner) 5 Fleet Place	
		City/State LONDON, EC4M 7RD	
		ZIP Code UK	FAX Number (if available) + 44 20 7571 8799
		Telephone Number +44 20 7575 0000	E-Mail Address (if available) intellectual.property@btgplc.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Anthony Tridico FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER		Address (of agent or representative named in 1.e.) 901 New York Avenue, NW	
		City/State WASHINGTON, DC	
		ZIP Code 20001-4413	FAX Number (if available) 202.408.4400
		Telephone Number 202.408.4000	E-Mail Address (if available) anthony.tridico@finnegan.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
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2. Drug Substance (Active Ingredient)	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
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2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.6 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	
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3.2 Does the patent claim only an intermediate?	
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4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
26, 27, 31 and 32	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) VARITHENA (1% polidocanol injectable microfoam) is indicated for 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. VARITHENA improves the symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system.
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
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Date Signed

12/20/2012

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Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Anthony Patrick Dolan	
Address BTG International Ltd, 5 Fleet Place	City/State London EC4M 7RD
ZIP Code UK	Telephone Number +44 20 7575 0000
FAX Number (if available) + 44 20 7571 8799	E-Mail Address (if available) Tony.Dolan@btgplc.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

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Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
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1. GENERAL			
a. United States Patent Number 6,572,873		b. Issue Date of Patent 06/03/2003	c. Expiration Date of Patent 05/26/2020
d. Name of Patent Owner BTG International Limited		Address (of Patent Owner) 5 Fleet Place	
		City/State LONDON, EC4M 7RD	
		ZIP Code UK	FAX Number (if available) + 44 20 7571 8799
		Telephone Number +44 20 7575 0000	E-Mail Address (if available) intellectual.property@btgplc.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Anthony Tridico FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER		Address (of agent or representative named in 1.e.) 901 New York Avenue, NW	
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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
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Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		
	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
1-9, 11-19	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) The solution is stored under a carbon dioxide atmosphere in an aluminum canister prior to use. This canister is activated with oxygen from a second canister to result in a final gas mixture of oxygen: carbon dioxide in a ratio of 65:35 with low nitrogen content. At the time of use, the VARITHENA is generated via the container system that produces microfoam of controlled density and bubble size.	
5. No Relevant Patents		
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.		<input type="checkbox"/> Yes

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<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
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Name Anthony Patrick Dolan	
Address BTG International Ltd, 5 Fleet Place	City/State London EC4M 7RD
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PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 205098	
		NAME OF APPLICANT/NDA HOLDER Provensis Ltd	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) VARITHENA			
ACTIVE INGREDIENT(S) injectable microfoam of carbon dioxide and oxygen gas and aqueous polidocanol solution		STRENGTH(S) 1% polidocanol solution in 35:65 carbon dioxide:oxygen gas mixture as a microfoam with liquid to gas ratio of 1:7 to provide 1.3 mg of polidocanol per mL of microfoam.	
DOSAGE FORM injectable microfoam			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 6,846,412		b. Issue Date of Patent 01/25/2005	c. Expiration Date of Patent 07/19/2022
d. Name of Patent Owner BTG International Limited		Address (of Patent Owner) 5 Fleet Place	
		City/State LONDON, EC4M 7RD	
		ZIP Code UK	FAX Number (if available) + 44 20 7571 8799
		Telephone Number +44 20 7575 0000	E-Mail Address (if available) intellectual.property@btgplc.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Anthony Tridico FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER		Address (of agent or representative named in 1.c.) 901 New York Avenue, NW	
		City/State WASHINGTON, DC	
		ZIP Code 20001-4413	FAX Number (if available) 202.408.4400
		Telephone Number 202.408.4000	E-Mail Address (if available) anthony.tridico@finnegan.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

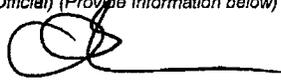
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

12/20/2012

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Anthony Patrick Dolan	
Address BTG International Ltd, 5 Fleet Place	City/State London EC4M 7RD
ZIP Code UK	Telephone Number +44 20 7575 0000
FAX Number (if available) + 44 20 7571 8799	E-Mail Address (if available) Tony.Dolan@btgplc.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 205098	
		NAME OF APPLICANT/NDA HOLDER Provensis Ltd	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
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FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 6,942,165		b. Issue Date of Patent 09/13/2005	c. Expiration Date of Patent 05/26/2020
d. Name of Patent Owner BTG International Limited		Address (of Patent Owner) 5 Fleet Place	
		City/State LONDON, EC4M 7RD	
		ZIP Code UK	FAX Number (if available) + 44 20 7571 8799
		Telephone Number +44 20 7575 0000	E-Mail Address (if available) intellectual.property@btgplc.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Anthony Tridico FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER		Address (of agent or representative named in 1.e.) 901 New York Avenue, NW	
		City/State WASHINGTON, DC	
		ZIP Code 20001-4413	FAX Number (if available) 202.408.4400
		Telephone Number 202.408.4000	E-Mail Address (if available) anthony.tridico@finnegan.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
4. Method of Use	
Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes

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Date Signed

12/20/2012

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Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Anthony Patrick Dolan	
Address BTG International Ltd, 5 Fleet Place	City/State London EC4M 7RD
ZIP Code UK	Telephone Number +44 20 7575 0000
FAX Number (if available) + 44 20 7571 8799	E-Mail Address (if available) Tony.Dolan@htgplc.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

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Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 205098	
		NAME OF APPLICANT/NDA HOLDER Provensis Ltd	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
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ACTIVE INGREDIENT(S) injectable microfoam of carbon dioxide and oxygen gas and aqueous polidocanol solution		STRENGTH(S) 1% polidocanol solution in 35:65 carbon dioxide:oxygen gas mixture as a microfoam with liquid to gas ratio of 1:7 to provide 1.3 mg of polidocanol per mL of microfoam.	
DOSAGE FORM injectable microfoam			
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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 7,025,290		b. Issue Date of Patent 04/11/2006	c. Expiration Date of Patent 05/26/2020
d. Name of Patent Owner BTG International Limited		Address (of Patent Owner) 5 Fleet Place	
		City/State LONDON, EC4M 7RD	
		ZIP Code UK	FAX Number (if available) + 44 20 7571 8799
		Telephone Number +44 20 7575 0000	E-Mail Address (if available) intellectual.property@btgplc.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Anthony Tridico FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER		Address (of agent or representative named in 1.e.) 901 New York Avenue, NW	
		City/State WASHINGTON, DC	
		ZIP Code 20001-4413	FAX Number (if available) 202.408.4400
		Telephone Number 202.408.4000	E-Mail Address (if available) anthony.tridico@finncgan.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) **1-10, 12-15, 17, 18** Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. *Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)*
 The solution is stored under a carbon dioxide atmosphere in an aluminum canister prior to use. This canister is activated with oxygen from a second canister to result in a final gas mixture of oxygen: carbon dioxide in a ratio of 65:35 with low nitrogen content. At the time of use, the VARITHENA is generated via the container system that produces microfoam of controlled density and bubble size.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification	
<p>6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed</p> <p>12/20/2012</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name</p> <p>Anthony Patrick Dolan</p>	
<p>Address</p> <p>BTG International Ltd, 5 Fleet Place</p>	<p>City/State</p> <p>London EC4M 7RD</p>
<p>ZIP Code</p> <p>UK</p>	<p>Telephone Number</p> <p>+44 20 7575 0000</p>
<p>FAX Number (if available)</p> <p>+ 44 20 7571 8799</p>	<p>E-Mail Address (if available)</p> <p>Tony.Dolan@btgplc.com</p>
<p>The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer 1350 Piccard Drive, Room 400 Rockville, MD 20850</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
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1. GENERAL			
a. United States Patent Number 7,357,336		b. Issue Date of Patent 04/15/2008	c. Expiration Date of Patent 05/26/2020
d. Name of Patent Owner BTG International Limited		Address (of Patent Owner) 5 Fleet Place	
		City/State LONDON, EC4M 7RD	
		ZIP Code UK	FAX Number (if available) + 44 20 7571 8799
		Telephone Number +44 20 7575 0000	E-Mail Address (if available) intellectual.property@btgplc.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Anthony Tridico FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER		Address (of agent or representative named in 1.e.) 901 New York Avenue, NW	
		City/State WASHINGTON, DC	
		ZIP Code 20001-4413	FAX Number (if available) 202.408.4400
		Telephone Number 202.408.4000	E-Mail Address (if available) anthony.tridico@finnegan.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

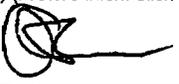
For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.	
2. Drug Substance (Active Ingredient)	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	
	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	
	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
	<input type="checkbox"/> Yes <input type="checkbox"/> No
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	
	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	
	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
	<input type="checkbox"/> Yes <input type="checkbox"/> No
4. Method of Use	
Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
1, 2, 7-12, 15-18, 20-23, 27-35	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) The solution is stored under a carbon dioxide atmosphere in an aluminum canister prior to use. This canister is activated with oxygen from a second canister to result in a final gas mixture of oxygen: carbon dioxide in a ratio of 65:35 with low nitrogen content. At the time of use, the VARITHENA is generated via the container system that produces microfoam of controlled density and bubble size.
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
	<input type="checkbox"/> Yes

6. Declaration Certification	
<p>6.1 <i>The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</i></p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)	Date Signed
	12/20/2012
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Anthony Patrick Dolan	
Address BTG International Ltd, 5 Fleet Place	City/State London EC4M 7RD
ZIP Code UK	Telephone Number +44 20 7575 0000
FAX Number (if available) + 44 20 7571 8799	E-Mail Address (if available) Tony.Dolan@btgplc.com
<p>The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer 1350 Piccard Drive, Room 400 Rockville, MD 20850</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 205098	
		NAME OF APPLICANT/NDA HOLDER Provensis Ltd	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) Varithena			
ACTIVE INGREDIENT(S) injectable microfoam of carbon dioxide and oxygen gas and aqueous polidocanol solution		STRENGTH(S) 1% polidocanol solution in 35:65 carbon dioxide:oxygen gas mixture as a microfoam with liquid to gas ratio of 1:7 to provide 1.3 mg of polidocanol per mL of microfoam.	
DOSAGE FORM injectable microfoam			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 7,604,185		b. Issue Date of Patent 10/20/2009	c. Expiration Date of Patent 05/26/2020
d. Name of Patent Owner BTG International Limited		Address (of Patent Owner) 5 Fleet Place	
		City/State LONDON, EC4M 7RD	
		ZIP Code UK	FAX Number (if available) + 44 20 7571 8799
		Telephone Number +44 20 7575 0000	E-Mail Address (if available) intellectual.property@btgplc.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Anthony Tridico FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER		Address (of agent or representative named in 1.e.) 901 New York Avenue, NW	
		City/State WASHINGTON, DC	
		ZIP Code 20001-4413	FAX Number (if available) 202.408.4400
		Telephone Number 202.408.4000	E-Mail Address (if available) anthony.tridico@finnegan.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.6 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
3.2 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
4. Method of Use	
Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
13-24	<input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) VARITHENA (1% polidocanol injectable microfoam) is indicated for 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. VARITHENA improves the symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system.
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
<input type="checkbox"/> Yes	

6. Declaration Certification	
<p>6.1 <i>The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</i></p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed</p> <p>12/20/2012</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name</p> <p>Anthony Patrick Dolan</p>	
<p>Address</p> <p>BTG International Ltd, 5 Fleet Place</p>	<p>City/State</p> <p>London EC4M 7RD</p>
<p>ZIP Code</p> <p>UK</p>	<p>Telephone Number</p> <p>+44 20 7575 0000</p>
<p>FAX Number (if available)</p> <p>+ 44 20 7571 8799</p>	<p>E-Mail Address (if available)</p> <p>Tony.Dolan@btgplc.com</p>
<p>The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer 1350 Piccard Drive, Room 400 Rockville, MD 20850</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>			
		NDA NUMBER 205098	
		NAME OF APPLICANT/NDA HOLDER Provensis Ltd	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) VARITHENA			
ACTIVE INGREDIENT(S) injectable microfoam of carbon dioxide and oxygen gas and aqueous polidocanol solution		STRENGTH(S) 1% polidocanol solution in 35:65 carbon dioxide:oxygen gas mixture as a microfoam with liquid to gas ratio of 1:7 to provide 1.3 mg of polidocanol per mL of microfoam.	
DOSAGE FORM injectable microfoam			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 7,731,986		b. Issue Date of Patent 06/08/2010	c. Expiration Date of Patent 11/17/2024
d. Name of Patent Owner BTG International Limited		Address (of Patent Owner) 5 Fleet Place	
		City/State LONDON, EC4M 7RD	
		ZIP Code UK	FAX Number (if available) + 44 20 7571 8799
		Telephone Number +44 20 7575 0000	E-Mail Address (if available) intellectual.property@btgplc.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Anthony Tridico FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER		Address (of agent or representative named in 1.e.) 901 New York Avenue, NW	
		City/State WASHINGTON, DC	
		ZIP Code 20001-4413	FAX Number (if available) 202.408.4400
		Telephone Number 202.408.4000	E-Mail Address (if available) anthony.tridico@finnegan.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) 25, 27	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input type="checkbox"/> No
--	---

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) VARITHENA is intended for intravenous injection using ultrasound guidance, administered via a single cannula into the lumen of the target incompetent trunk veins or by direct injection into varicosities. The maximum recommended microfoam volume per treatment session is 15 mL, divided into aliquots of up to 5 mL.
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5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

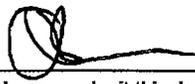
6. Declaration Certification

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



12/20/2012

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Anthony Patrick Dolan	
Address BTG International Ltd, 5 Fleet Place	City/State London EC4M 7RD
ZIP Code UK	Telephone Number +44 20 7575 0000
FAX Number (if available) + 44 20 7571 8799	E-Mail Address (if available) Tony.Dolan@btgplc.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 205098	
		NAME OF APPLICANT/NDA HOLDER Provensis Ltd	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) VARITHENA			
ACTIVE INGREDIENT(S) injectable microfoam of carbon dioxide and oxygen gas and aqueous polidocanol solution		STRENGTH(S) 1% polidocanol solution in 35:65 carbon dioxide:oxygen gas mixture as a microfoam with liquid to gas ratio of 1:7 to provide 1.3 mg of polidocanol per mL of microfoam.	
DOSAGE FORM injectable microfoam			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 7,814,943		b. Issue Date of Patent 10/19/2010	c. Expiration Date of Patent 11/19/2027
d. Name of Patent Owner BTG International Limited		Address (of Patent Owner) 5 Fleet Place	
		City/State LONDON, EC4M 7RD	
		ZIP Code UK	FAX Number (if available) + 44 20 7571 8799
		Telephone Number +44 20 7575 0000	E-Mail Address (if available) intellectual.property@btgplc.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Anthony Tridico FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER		Address (of agent or representative named in T.e.) 901 New York Avenue, NW	
		City/State WASHINGTON, DC	
		ZIP Code 20001-4413	FAX Number (if available) 202.408.4400
		Telephone Number 202.408.4000	E-Mail Address (if available) anthony.tridico@finnegan.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) 26, 27, 28	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input type="checkbox"/> No
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4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) The solution is stored under a carbon dioxide atmosphere in an aluminum canister prior to use. This canister is activated with oxygen from a second canister to result in a final gas mixture of oxygen: carbon dioxide in a ratio of 65:35 with low nitrogen content. At the time of use, the VARITHENA is generated via the container system that produces microfoam of controlled density and bubble size. The microfoam is then transferred to a syringe through a MTU. Also as described in IFU.
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5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification	
<p>6.1 <i>The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</i></p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed
	12/20/2012
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
Check applicable box and provide information below.	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Anthony Patrick Dolan	
Address BTG International Ltd, 5 Fleet Place	City/State London EC4M 7RD
ZIP Code UK	Telephone Number +44 20 7575 0000
FAX Number (if available) + 44 20 7571 8799	E-Mail Address (if available) Tony.Dolan@btgplc.com
<p>The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer 1350 Piccard Drive, Room 400 Rockville, MD 20850</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 205098	
		NAME OF APPLICANT/NDA HOLDER Provensis Ltd	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) VARITHENA			
ACTIVE INGREDIENT(S) injectable microfoam of carbon dioxide and oxygen gas and aqueous polidocanol solution		STRENGTH(S) 1% polidocanol solution in 35:65 carbon dioxide:oxygen gas mixture as a microfoam with liquid to gas ratio of 1:7 to provide 1.3 mg of polidocanol per mL of microfoam.	
DOSAGE FORM injectable microfoam			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 7,842,282		b. Issue Date of Patent 11/30/2010	c. Expiration Date of Patent 05/26/2020
d. Name of Patent Owner BTG International Limited		Address (of Patent Owner) .5 Fleet Place	
		City/State LONDON, EC4M 7RD	
		ZIP Code UK	FAX Number (if available) + 44 20 7571 8799
		Telephone Number +44 20 7575 0000	E-Mail Address (if available) intellectual.property@btgplc.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Anthony Tridico FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER		Address (of agent or representative named in 1.e.) 901 New York Avenue, NW	
		City/State WASHINGTON, DC	
		ZIP Code 20001-4413	FAX Number (if available) 202.408.4400
		Telephone Number 202.408.4000	E-Mail Address (if available) anthony.tridico@finnegan.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.6 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
3.2 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
4. Method of Use	
Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
1-20	<input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) VARITHENA (1% polidocanol injectable microfoam) is indicated for 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. VARITHENA improves the symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system.
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
<input type="checkbox"/> Yes	

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed</p> <p>12/20/2012</p>
--	--------------------------------------

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name Anthony Patrick Dolan</p>	
<p>Address BTG International Ltd, 5 Fleet Place</p>	<p>City/State London EC4M 7RD</p>
<p>ZIP Code UK</p>	<p>Telephone Number +44 20 7575 0000</p>
<p>FAX Number (if available) + 44 20 7571 8799</p>	<p>E-Mail Address (if available) Tony.Dolan@btgplc.com</p>

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 205098	
		NAME OF APPLICANT/NDA HOLDER Provensis Ltd	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) VARITHENA			
ACTIVE INGREDIENT(S) injectable microfoam of carbon dioxide and oxygen gas and aqueous polidocanol solution		STRENGTH(S) 1% polidocanol solution in 35:65 carbon dioxide:oxygen gas mixture as a microfoam with liquid to gas ratio of 1:7 to provide 1.3 mg of polidocanol per mL of microfoam.	
DOSAGE FORM injectable microfoam			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 7,842,283		b. Issue Date of Patent 11/30/2010	c. Expiration Date of Patent 05/26/2020
d. Name of Patent Owner BTG International Limited		Address (of Patent Owner) 5 Fleet Place	
		City/State LONDON, EC4M 7RD	
		ZIP Code UK	FAX Number (if available) + 44 20 7571 8799
		Telephone Number +44 20 7575 0000	E-Mail Address (if available) intellectual.property@btgplc.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Anthony Tridico FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER		Address (of agent or representative named in 1.e.) 901 New York Avenue, NW	
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		ZIP Code 20001-4413	FAX Number (if available) 202.408.4400
		Telephone Number 202.408.4000	E-Mail Address (if available) anthony.tridico@finnegan.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?			
		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?			
		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed
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Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Anthony Patrick Dolan	
Address BTG International Ltd, 5 Fleet Place	City/State London EC4M 7RD
ZIP Code UK	Telephone Number +44 20 7575 0000
FAX Number (if available) + 44 20 7571 8799	E-Mail Address (if available) Tony.Dolan@btgplc.com

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Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

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Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 205098	
		NAME OF APPLICANT/NDA HOLDER Provensis Ltd	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) VARITHENA			
ACTIVE INGREDIENT(S) injectable microfoam of carbon dioxide and oxygen gas and aqueous polidocanol solution		STRENGTH(S) 1% polidocanol solution in 35:65 carbon dioxide:oxygen gas mixture as a microfoam with liquid to gas ratio of 1:7 to provide 1.3 mg of polidocanol per mL of microfoam.	
DOSAGE FORM injectable microfoam			
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For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 8,122,917		b. Issue Date of Patent 02/28/2012	c. Expiration Date of Patent 09/09/2024
d. Name of Patent Owner BTG International Limited		Address (of Patent Owner) 5 Fleet Place	
		City/State LONDON, EC4M 7RD	
		ZIP Code UK	FAX Number (if available) + 44 20 7571 8799
		Telephone Number +44 20 7575 0000	E-Mail Address (if available) intellectual.property@btgplc.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Anthony Tridico FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER		Address (of agent or representative named in 1.e.) 901 New York Avenue, NW	
		City/State WASHINGTON, DC	
		ZIP Code 20001-4413	FAX Number (if available) 202.408.4400
		Telephone Number 202.408.4000	E-Mail Address (if available) anthony.tridico@finnegan.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

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2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input type="checkbox"/> No
--	---

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
---	--

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

12/20/2012

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Anthony Patrick Dolan	
Address BTG International Ltd, 5 Fleet Place	City/State London EC4M 7RD
ZIP Code UK	Telephone Number +44 20 7575 0000
FAX Number (if available) + 44 20 7571 8799	E-Mail Address (if available) Tony.Dolan@btgplc.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>			
TRADE NAME (OR PROPOSED TRADE NAME) VARITHENA		NDA NUMBER 205098	
ACTIVE INGREDIENT(S) injectable microfoam of carbon dioxide and oxygen gas and aqueous polidocanol solution		STRENGTH(S) 1% polidocanol solution in 35:65 carbon dioxide:oxygen gas mixture as a microfoam with liquid to gas ratio of 1:7 to provide 1.3 mg of polidocanol per mL of microfoam.	
DOSAGE FORM injectable microfoam			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 8,323,677		b. Issue Date of Patent 12/04/2012	c. Expiration Date of Patent 05/26/2020
d. Name of Patent Owner BTG International Limited		Address (of Patent Owner) 5 Fleet Place	
		City/State LONDON, EC4M 7RD	
		ZIP Code UK	FAX Number (if available) + 44 20 7571 8799
		Telephone Number +44 20 7575 0000	E-Mail Address (if available) intellectual.property@btgplc.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Anthony Tridico FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER		Address (of agent or representative named in 1.e.) 901 New York Avenue, NW	
		City/State WASHINGTON, DC	
		ZIP Code 20001-4413	FAX Number (if available) 202.408.4400
		Telephone Number 202.408.4000	E-Mail Address (if available) anthony.tridico@finnegan.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.		
2. Drug Substance (Active Ingredient)		
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)		
	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?		
	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)		
	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3. Drug Product (Composition/Formulation)		
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?		
	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?		
	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)		
	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4. Method of Use		
<i>Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:</i>		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		
	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)	
5. No Relevant Patents		
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.		<input type="checkbox"/> Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

12/20/2012

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Anthony Patrick Dolan	
Address BTG International Ltd, 5 Fleet Place	City/State London EC4M 7RD
ZIP Code UK	Telephone Number +44 20 7575 0000
FAX Number (if available) + 44 20 7571 8799	E-Mail Address (if available) Tony.Dolan@btgplc.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 205098

SUPPL #

HFD #

Trade Name Varithena

Generic Name polidocanol

Applicant Name Provensis

Approval Date, If Known November 25, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021201

Asclera (polidocanol)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 015
Study 016

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 015

Study 016

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 063420 YES !
! NO
! Explain:

Investigation #2
IND # 063420 YES !
! NO
! Explain:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

APPEARS THIS WAY ON ORIGINAL



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

/s/

MICHAEL V MONTELEONE
11/25/2013

NORMAN L STOCKBRIDGE
11/25/2013

1.3. Administrative Information

3. DEBARMENT CERTIFICATION

Protherics Ltd. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Andreia Collier, MSc
Vice President, Regulatory Affairs

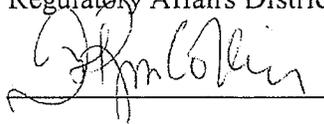
21 DEC 2012

Date

1.3. Administrative Information

2. FIELD COPY CERTIFICATION

As this application has been submitted electronically, a field copy of the application has not been provided to the FDA District Office. Per FDA Guidance, "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" (2006), documentation need not be provided to the FDA Office of Regulatory Affairs District Office.



Andreia Collier, MSc
Vice President, Regulatory Affairs

21 Dec 2012

Date

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

/s/

MARY GRACE LUBAO
12/03/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205098 BLA #	NDA Supplement # N/A BLA Supplement #	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Varithena Established/Proper Name: polidocanol Dosage Form: injectable foam		Applicant: Provensis Agent for Applicant (if applicable): BTG International
RPM: Michael Monteleone		Division: Cardiovascular and Renal Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>December 4, 2013</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC <input type="checkbox"/> Breakthrough Therapy designation </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 2013-11-25
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Yes
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Yes
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	Yes
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	Acceptable 2013-06-18 Review 2013-06-18
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 2013-10-01 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 2013-11-22 <input checked="" type="checkbox"/> OPDP (DDMAC) 2013-10-31 <input checked="" type="checkbox"/> SEALD 2013-11-22 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	2013-04-11
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>2013-10-30</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 2012-03-26 2012-07-31
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 2009-06-29
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2013-11-25
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2013-11-14
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	2013-07-12
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See pg 17 of Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 2013-06-28
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2013-07-02
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2013-07-02
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2013-10-30
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2013-10-30
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2013-09-05
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2013-09-05
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 2013-11-25
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 2013-03-18 – BioPhar 2013-08-30 – ONDQA #1 2013-11-07 – ONDQA #2 2013-11-25 – ONDQA #3
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 2013-09-12
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None 2013-04-24 CDRH HF#1 2013-07-26 CDRH MS 2013-08-08 CDRH Engineering 2013-10-17 CDRH HF#2 2013-11-14 CDRH HF#3
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	2013-08-24
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: 2013-11-22 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

MICHAEL V MONTELEONE
11/25/2013

Bouie, Teshara

From: Bouie, Teshara
Sent: Thursday, November 07, 2013 10:20 AM
To: Simon Leppard (Simon.Leppard@biocompatibles.com)
Cc: Monteleone, Michael V.; Andreia Collier (Andreia.Collier@btgplc.com)
Subject: NDA 205098 - Information Request

Hi Simon,

We acknowledge your revised content uniformity proposal submitted on October 18, 2013. The combination of assay and extractable volume as a measure of content uniformity is acceptable. The proposal addresses testing for content uniformity through the canister life and across canisters in a given batch. However, the proposal does not include a control for content uniformity of the entire batch. After review of your proposal, we recommend the following revisions to ensure the content uniformity testing assesses content uniformity through the life of individual canisters, across canisters in a given batch, and across batches:

- Update Section 3.2.P.3.3 and all other relevant sections to reflect the in-process control and associated acceptance criterion for content uniformity of canisters across the fill run for each batch.
- Update Section 3.2.P.5 and all other relevant sections to include a test for content uniformity of the batch with appropriate acceptance criteria in addition to the test for content uniformity through the canister life with appropriate acceptance criteria. We recommend testing a sufficient number of canisters from the batch to determine the batch content uniformity. Canisters from the batch content uniformity test samples may be used to conduct testing for content uniformity through canister life. The proposed (b) (4) for the through canister life content uniformity testing is acceptable.
- Update Section 3.2.P.8.2 and all other relevant sections to include both the batch content uniformity and content uniformity through canister life tests as part of the stability protocol at Month 0, Month 3, Month 6, Month 12, and Month 18.

Regards,

Teshara G. Bouie, MSA, OTR/L

CDR, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment I
Phone (301) 796-1649
Fax (301) 796-9749

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

/s/

TESHARA G BOUIE
11/07/2013



NDA 205098

INFORMATION REQUEST

Provenis Ltd.
c/o BTG International Inc.
Attention: Pamela Deans, Senior Manager of Regulatory Affairs
Five Tower Bridge, Suite 800
300 Barr Harbor Drive
West Conshohocken, PA 19428

Dear Ms. Deans:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Polidocanol Injectable Foam.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide the amount of (b)(4) extracted from the commercial (Version 4) and development (Version 3.2) (b)(4) on a mcg/g basis. The submission lacks sufficient details about the extraction method to determine the actual content of (b)(4) extracted from the (b)(4)
2. (b)(4)
3. Provide justification for referring to the Ph. Eur. standards for ethanol and hydrochloric acid instead of the corresponding USP standards for the monographs where a USP standard exists. Provide a copy of the Ph. Eur. standard for each excipient that references a Ph. Eur. standard. Provide a statement acknowledging the corresponding USP monograph as the official standard and the corresponding analytical procedures as the regulatory analytical method.
4. Identify which method under USP <788> Particulate Matter in Injections is used for the sub-visible particulates analytical procedure. USP <788> includes two tests – Method I (light obscuration) and Method II (microscopic). The information provided in the submission did not identify which method is used during testing. If the sub-visible particulate analytical procedure follows Method II (microscopic), provide justification for relying on this method instead of the preferred Method I (light obscuration).

5. Update Section 3.2.R.3 of the submission to remove the ADTR191 Comparability Protocol. As noted in our initial comment, inclusion of a previously executed comparability protocol in this section is not appropriate. Section 3.2.R.3 is reserved for proposed comparability protocols supporting post-marketing changes.
6. We recommend the following revisions for the immediate polidocanol container label:
 - Delete the duplicate “which” on line two of the contents section
 - Include all ingredients and their respective amounts in the contents section
 - Move the drug product expression of strength after the established name
 - Revise the storage temperature statement based on the USP controlled room temperature statement
 - Remove [REDACTED] (b) (4) from the label; This statement is not required for injections
 - Delete [REDACTED] (b) (4) from the avoid contact statement; The drug product [REDACTED] (b) (4) during intravenous administration
7. We recommend the following revisions for the immediate oxygen container label:
 - Move the drug product expression of strength after the established name
 - Add the net content along with all ingredients and their respective amounts to the contents section
 - Add “do not resterilize” to the sterile contents statement
 - Add a statement indicating the recommended storage temperature, including the instruction “Do not refrigerate or freeze” on the label
 - Include the instructions “For dosage and administration read the PI and IFU” and “Avoid contact with eyes” on the label
 - Include the lot number, expiration date, NDC number, and bar code for the oxygen canister on the label
8. We recommend the following revisions to the bi-canister pouch label:
 - Move the drug product expression of strength after the established name
 - Include all ingredients and their respective amounts in the contents section
 - Revise the storage temperature statement based on the USP controlled room temperature statement
 - Include the instructions “For dosage and administration read the PI and IFU”, “Avoid contact with eyes”, and “Do not shake” on the label
 - Remove [REDACTED] (b) (4) from the label; This statement is not required for injections
9. We recommend the following revisions to the bi-canister pouch carton label:
 - Move the drug product expression of strength after the established name
 - Include all ingredients and their respective amounts in the contents section
 - Revise the storage temperature statement based on the USP controlled room temperature statement
 - Include the instructions “For dosage and administration read the PI and IFU”, “Avoid contact with eyes”, and “Do not shake” on the label
 - Remove [REDACTED] (b) (4) from the label; This statement is not required for injections

10. We recommend the following revisions to the MTU immediate container label:

- Move the drug product expression of strength after the established name
- Revise the storage temperature statement based on the USP controlled room temperature statement
- Include the instruction “For dosage and administration read the PI and IFU” on the label
- Include a barcode for the MTU on the label
- Remove [REDACTED] (b) (4) from the label; This statement is not required for injections

11. We recommend the following revisions to the administration box label:

- Move the drug product expression of strength after the established name
- Include the instruction “Sterile contents: do not resterilize” on the label; Both the syringe and manometer tubing included in the administration box are sterile products
- Include the instructions “For dosage and administration read the PI and IFU” and “To be used in conjunction with Varithena only” on the label
- Add a statement indicating the recommended storage temperature on the label
- Include the lot number and a barcode for the administration box on the label

12. We recommend the following revisions to the commercial box label:

- Move the drug product expression of strength after the established name
- Include all ingredients and their respective amounts in the contents section
- Revise the storage temperature statement based on the USP controlled room temperature statement
- Include the instructions “Do not resterilize,” “Avoid contact with eyes,” and “Do not shake” on the label

13. As [REDACTED] (b) (4) is not a recognized dosage form by either FDA or USP, the proposed established name is not acceptable. Even if approval of [REDACTED] (b) (4) by USP is granted this review cycle, the Agency, including the Labeling and Nomenclature Committee, will need to evaluate the use of the dosage form. As a path forward, we recommend consideration of the use of an approved dosage form in the established name.

FDA Response to Request for Advice Included in the July 9, 2013 Amendment

1. We agree with the proposal to control assay at release based on the overall response from the polidocanol oligomers. Update the relevant sections of the submission to reflect the change in analytical procedure, including the regulatory drug substance specification. Include an appropriate acceptance criterion for the new assay method in the revised specification.

If you have any questions, contact Yvonne Knight, Regulatory Project Manager, at (301) 796-2133.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Acting Division Director
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
09/05/2013

Bouie, Teshara

From: Bouie, Teshara
Sent: Monday, August 12, 2013 12:25 PM
To: Andreia Collier (Andreia.Collier@btgplc.com)
Cc: Monteleone, Michael V.
Subject: NDA 205098 - Information Request

Hi Andreia,

We have the following request for information:

The results of studies summarized in section 3.2.P.2.5 of NDA 205-098 demonstrate that Polidocanol Injectable Microfoam does not meet the acceptance criteria for USP <51> Antimicrobial Effectiveness testing and may support the growth of microorganisms after a period of approximately (b) (4). Although the product is sterile, maintained under positive pressure, and the fluid path is shielded with the microfoam transfer unit (MTU), the product path will be exposed to the environment intermittently during normal product use. Therefore, additional precautions must be taken in order to reduce the risk of microbial contamination and growth along the product path during the proposed 7-day in-use period.

Please amend the physician training materials to state that the stem of the shuttle filter assembly should be swabbed with a sterile alcohol pad just prior to the attachment of each new MTU in order to reduce the risk of microbial contamination along the product path during the in-use period.

Regards,

Teshara G. Bouie, MSA, OTR/L
CDR, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment I
Phone (301) 796-1649
Fax (301) 796-9749

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/s/

TESHARA G BOUIE
08/12/2013



NDA 205098

INFORMATION REQUEST

Provenis Ltd.
c/o BTG International Inc.
Attention: Heather McIntosh, Regulatory Operations Manager
Five Tower Bridge, Suite 800
300 Barr Harbor Drive
West Conshohocken, PA 19428

Dear Ms. McIntosh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Polidocanol Injectable Foam.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Revise the composition table to include the amount of each component on a % w/w basis. The table provided includes amount per mL and amount per unit only.
2. Compare the amount of each excipient, including the gases, in the formulation to the FDA inactive ingredient database limit for this route of administration based on the maximum daily dose for the drug product. If any excipient amount in the drug product exceeds the database limit, provide justification, supported by data, to demonstrate that the proposed excipient level is considered safe for human use.
3. Provide justification for the (b) (4) for the formulation excipients or revise the composition table to reflect a fixed commercial formulation. The master batch record indicates that a fixed formulation is used during production. The composition of the clinical trial formulations indicates that fixed amounts of excipients were used as well.
4. Provide the weight of the (b) (4) proposed for the commercial drug product and the weight of the (b) (4) used during clinical studies. Provide the weight of the (b) (4) used during clinical studies. This information was not easily identified in the submission.
5. Clarify if the category "other PNAs" includes the observed content of (b) (4) Varisolve (b) (4) Development Report PDE008-02 (Page 23 of 55) noted (b) (4) as the major extractables of Version 3.2 of the (b) (4)

(b) (4) However, the data presented in Section 3.2.P.4.9.1-Table 71 does not include the contents for the (b) (4) extractables.

6. Update the drug product process description to include information on the temperature controls employed during the (b) (4).
The only detail provided in the current process description states that the polidocanol (b) (4). The current process description does not include any details regarding (b) (4) and how it is controlled (b) (4).
7. Comment on the potential for polidocanol (b) (4).
The process description did not include any details regarding (b) (4) during the (b) (4). The submission did not include any data to demonstrate that the amount of ethanol in the solution is sufficient to (b) (4).
8. Clarify if the ethanol and hydrochloric acid specifications comply with the current USP/NF monograph requirements. Table 1 in Section 3.2.P.1 indicates that these excipients comply with the USP/NF monograph but Table 1 in Section 3.2.P.4 indicates that these excipients comply with the Ph.Eur. monographs.
9. Revise the visible particulates acceptance criterion to “Free from visible particulates.” The use of (b) (4) in the criterion is not acceptable. The solution should be free from all visible particles at release and on stability.
10. Revise the total degradation products acceptance criterion. The batch analysis and stability results provided in the submission do not support a limit of NMT (b) (4). The maximum total degradation product reported in the primary stability batches was (b) (4) and the maximum reported for the site specific batches was (b) (4).
11. Revise the proposed content uniformity acceptance criteria to include controls that ensure that patient receive the same polidocanol content via microfoam with similar properties when receiving treatment from the beginning, middle, and end of the canister at release and over the drug product shelf-life. The proposed acceptance criteria are inadequate as they only the total content and volume of the canister.
12. Provide justification for referring to the Ph. Eur. standards instead of the corresponding USP standards for the visible particulate analytical procedure used to test the drug product as well as the identity and endotoxin tests used to release the incoming drug substance. Provide a copy of the Ph. Eur. standard for each test that references a Ph. Eur. standard. Provide a statement acknowledging the corresponding USP method as the official standard and the corresponding analytical procedures as the regulatory analytical method.

13. Provide a detailed description of the (b) (4) analytical procedure, including a diagram of the (b) (4) apparatus. The information provided in the submission is not adequate to fully assess the proposed analytical procedure.
14. Identify the (b) (4) for the oxygen canister prior to testing associated with analytical procedure TM 363 Canister Gas Pressure. The submission did not specify the (b) (4).
15. Provide validation results for the (b) (4) analytical procedures based on method validation against pre-specified validation criteria for the parameters tested. We do not consider these analytical procedures validated due to the lack of pre-specified validation criteria.
16. Provide justification for not conducting robustness validation activities (b) (4).
(b) (4) These analytical procedures may be impacted by small variations in experimental conditions.
17. Provide the batch analysis results for oligomer profile, average oligomer, extractable volume, ethanol content, canister pressure (polidocanol and oxygen) for all 1% strength drug products used in clinical studies VV008, VV015, and VV016. The batch analysis results provided in the submission do not includes results for these test parameters.
18. Provide the batch size, date of manufacture, site of manufacture, drug substance lot used during manufacturing, and batch analysis results for clinical drug product lots 0909018 and 0922012. These lots were identified as drug product lots used during Phase III (Study VV015) in Section 3.2.P.2.2.1.6 – Table 6 but the requested information was not easily located in the submission.
19. Identify the use of drug product lot 0902002. The clinical analysis results in Section 3.2.P.5.4.4 – Table 11 include results for lot 0902002 but this lot was not included in the list of drug products used in clinical studies (Section 2.3.P.2.2.1.2 – Table 2).
20. Provide justification for not including controls for foam expansion rate, foam residence time, foam plug volume, and foam degradation rate in the proposed regulatory drug product specification. Section 3.2.P.2.2.3 of the submission identified these properties as quantifiable properties of foam behavior that were evaluated to assess foam cohesiveness, an attribute critical to the safety and efficacy of the drug product.
21. Revise the post-approval and annual stability protocol to indicate that at least one (1) drug product batch will be included in the stability program every year at least one drug product batch is manufactured. Section 1.0 of the protocol indicates that one batch will be added to the stability program annually for only three years. It is our expectation that at least one batch of drug product will be added to the stability program for each year that drug product is manufactured as continued assurance of drug product quality over the shelf-life.

22. Revise the post-approval and annual stability protocol to include testing of the accelerated condition samples at the initial time point. The current test schedule only includes testing at Month 3 and Month 6. Testing at the initial time point should be included as well. In addition, provide justification for not including content uniformity as part of the accelerated condition test schedule for the post-approval and annual stability protocol.
23. Revise the registered drug product specification (document reference FAR-13-PS001) to include acceptance criterion for aluminum. The post-approval and annual stability protocol in Section 3.2.P.8.2 indicates that aluminum content will be tested for the post-approval and annual stability batches. However, the drug product specification included in Section 3.2.P.5.1 does not include a test or criterion for aluminum content. Revise the specification in Section 3.2.P.5.1 to include the aluminum test and to indicate all tests intended for stability testing.
24. Provide a summary of the stability studies and stability results for 1% strength drug product lots used during clinical studies VV008, VV015, and VV016. If available, also include results for any in-use stability studies conducted with these lots. The submission included batch analysis results for these lots but did not appear to include stability data.
25. Provide in-use stability data based on a (b) (4) in-use period. Assess the impact of a (b) (4) in-use period on available samples of the oldest available stability samples. This information is requested to support our evaluation of a suitable in-use period for the drug product.
26. Provide justification for not monitoring canister pressure for either the polidocanol or oxygen canisters during the 7-Day in-use stability studies. The submission did not clearly indicate why these tests were omitted from the 7-Day in-use stability study protocol.
27. Clarify if Comparability Protocol ADTR191 included in the submission will be executed post-approval or if it was previously executed to demonstrate equivalency of the drug product manufacturing sites for NDA submission. If this protocol was previously executed, inclusion in Section 3.2.R.3 of the submission is not appropriate. The protocol can be included in Section 3.2.P.2.3 as an appended document for reference.
28. Update the methods validation package (Section 3.2.R.2) to include reference to the drug product composition and identify the samples, by lot/batch number, that are included in the package. Also include a statement that certificate of analyses (CoAs) and material safety data sheets (MSDSs) will be provided with samples. The submission does not include the requested information. Refer to FDA Guidance Guidelines for Submitting Samples and Analytical Data for Methods Validation for additional information (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm123124.htm>).

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Acting Division Director
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
07/18/2013



NDA 205098

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Provensis Ltd.
c/o BTG International, Inc.
Five Tower Bridge, Suite 800
300 Barr Harbor Drive
West Conshohocken, PA 19428

ATTENTION: Heather McIntosh
Regulatory Operations Manager

Dear Ms. McIntosh:

Please refer to your New Drug Application (NDA) dated February 1, 2013, received February 4, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Polidocanol Injectable Microfoam, 1%.

We also refer to your correspondence, dated and received March 21, 2013, requesting review of your proposed proprietary name, Varithena. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Varithena, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. If **any** of the proposed product characteristics as stated in your March 21, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cheryle Milburn, Safety Regulatory Project Manager, in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact Michael Monteleone, the Office of New Drugs (OND) Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
06/18/2013



NDA 205098

INFORMATION REQUEST

Provenis Ltd.
c/o BTG International Inc.
Attention: Heather McIntosh, Regulatory Operations Manager
Five Tower Bridge, Suite 800
300 Barr Harbor Drive
West Conshohocken, PA 19428

Dear Ms. McIntosh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Polidocanol Injectable Foam.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. Provide details about how the (b) (4) supplier controls identity. We note the safety risk associated with sampling (b) (4) on site to confirm the identity. Therefore, the supplier should confirm identity and include the results on the certificate of analysis.
2. Revise the (b) (4) material specifications to include criterion for identity. The proposed specifications do not include controls for material identification.
3. Revise Section 3.2.S.2.3 of the submission to include the material specification for the (b) (4). We note that the material is accepted based on the supplier's certificate of analysis. However, the material specification should still be included in this section of the submission.
4. Provide justification, supported by applicable data, for not implementing the recommendations from the process parameter evaluation report concerning a limit for (b) (4) starting material and a limit for (b) (4) in the final drug substance for the proposed commercial process. Our review of the information supporting the proposed commercial drug substance manufacturing process determined that four of the six original recommendations were implemented.

We could not identify evidence that the process incorporates the proposed controls for (b) (4)

5. Revise the drug substance specification to include a test for polidocanol assay with appropriate acceptance criterion. We note the specification includes a test for % purity. However, the stability protocol includes a test for polidocanol assay. We consider assay a more appropriate control for strength whereas we consider % purity an additional measure for impurity content.
6. Revise the limit for single identified impurities to (b) (4) in accordance with ICH Q3A. Revise the limit for single unidentified impurity to “Any single unidentified impurity (b) (4).” Revise the (b) (4) limit to “Any (b) (4) (b) (4).” The proposed representation of these limits is not consistent with how similar limits are represented in the specification, which may lead to confusion.
7. Revise the acceptance criteria associated with Method TM 217 (b) (4) (b) (4) to include the limit for (b) (4). The method description and validation indicate that this test controls the content of both (b) (4) (b) (4).
8. Include a limit for related (b) (4) in the drug substance specification or provide justification, supported by data, for omitting this test. The impurities characterization studies indicate that (b) (4) degradants were observed at release and during stability testing of the polidocanol batches.
9. Provide justification for omitting tests for refractive index, solubility, viscosity, density, and melting range in the drug substance specification. The drug substance characterization studies during process development indicated that these physiochemical properties can potentially impact polidocanol’s surfactant action.
10. Provide justification for referring to the Ph. Eur. standards instead of the corresponding USP standards for the analytical procedures where a USP standard exists. Provide a copy of the Ph. Eur. standard for each test that references a Ph. Eur. standard. Provide a statement acknowledging the corresponding USP method as the official standard and the corresponding analytical procedures as the regulatory analytical method.
11. Provide a brief summary for the appearance of solution analytical procedure in Section 3.2.S.4.2. The submission includes brief summaries of all analytical procedures based on compendial methods except the appearance of solution method.
12. Provide results for (b) (4) (b) (4) content by Method 217 for the registration stability batches as well as drug substance batches used in clinical and nonclinical studies. The batch analysis results provided in the submission did not include values for these drug substance release tests.

13. Identify the specific container closure used to store the samples tested to generate the drug substance registration stability data. Section 5.0 of the registration stability batch protocol indicates that [REDACTED] (b) (4). However, Appendix 1 of the protocol lists three different fill amounts and three different bottles.
14. We determined that a [REDACTED] (b) (4) retest period is most appropriate for the polidocanol drug substance based on our review of the data submitted. The limited amount of submitted data does not allow for extrapolation of data. You may submit long-term and accelerated stability data from the Month 6 time point, if available, to further support your proposed [REDACTED] (b) (4) interim retest period.
15. Clarify the reporting units for the endotoxins test during stability testing. The release specification lists the reporting unit as EU/g but the reporting unit used during stability was IU/g.
16. Provide results from the confirmatory photostability test for polidocanol drug substance. ICH Q1B Photostability Testing of New Drug Substances and Products indicates that for drug substances, photostability testing should consist of two parts – forced degradation and confirmatory testing. The confirmatory photostability test should comply with the requirements outlined in ICH Q1B.

Drug Product

17. Provide a summary of the interactions with the United States Pharmacopeia, including any official correspondence, regarding the establishment of [REDACTED] (b) (4) as a dosage form. We were not able to identify any evidence in the submission that supports the use of [REDACTED] (b) (4) as the recognized dosage form.

If you have any questions, contact Yvonne Knight, Regulatory Project Manager, at (301) 796-2133.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
05/31/2013



NDA 205098

FILING COMMUNICATION

Provensis Ltd
Attention: Andreia Collier
5 Fleet Place
London
EC4M 7RD
UK

Dear Ms. Collier:

Please refer to your New Drug Application (NDA) dated February 1, 2013, received February 4, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for polidocanol injectable foam 1%.

We also refer to your amendments dated February 13, 28, March 5, 6, 11, 13, 18, 21 and April 8, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 4, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 4, 2013.

We request that you submit the following information:

Chemistry

1. In order to facilitate our review of the design and function of the drug product, please submit samples of the to-be-marketed drug product. Functioning samples containing the commercial formulation or a representative surrogate formulation are desired over empty demonstration samples.
2. Please provide the (b) (4) procedure and the results of validation studies for all container closure components contacting the drug product.
3. Please provide the results of the 12/24/36-hour modified antimicrobial effectiveness test on polidocanol referred to in section 3.2.P.2.5 of the application.

SEALD

4. Please provide full transcripts and saturation grids for both the VVSymQ and the PA-V3.
5. Please provide a description of the data management process for electronic data collected by electronic diary to show that maintenance, transmission, and storage of electronic source documents comply with regulatory requirements.
6. Please provide the user manual and/or training guide for patients and investigators for the electronic diary.

DRISK

7. The Division of Risk Management is reviewing your proposed risk management plan. Your proposal suggests there are risks associated with polidocanol that may require mitigation strategies beyond labeling and routine pharmacovigilance (e.g., elements to assure safe use). If you feel additional risk mitigation is necessary to assure safe use of polidocanol, please refer to the following Guidance for Industry for the correct format and content for your proposal and resubmit accordingly.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>.
Furthermore, we note that your proposed risk management plan includes a list of training forms and materials. In order to facilitate an efficient review of a proposed risk mitigation plan, all materials identified within the proposal that will be necessary to implement the plan should be submitted.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Under Highlights

1. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each bullet.
Advice: Add references for Drug Interactions, Use in Specific Populations

2. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Advice: Add pharmacologic class, 'sclerosing agent'

Under Table of Contents

3. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Advice: Capitalize Full Prescribing Information

Under Full Prescribing Information

4. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Advice: Follow above formatting scheme for cross references.

5. Review and ensure that font type and size is consistent throughout the body of the Full Prescribing Information.

We request that you resubmit labeling that addresses these issues by April 25, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
04/11/2013

From: [Mesmer, Deborah](#)
To: ["Andreia Collier"](#)
Cc: [Monteleone, Michael V.](#)
Subject: NDA 205098 Information Request 03/06/13
Date: Wednesday, March 06, 2013 11:23:21 AM

Dear Ms. Collier,

Please refer to NDA 205098 for polidocanol injectable foam 1%.

We have the following requests:

Your firm has provided a summary of the manufacturing sites involved in the production of their device, and a summary of the activities performed at each site. However, it is unclear what manufacturing activities are performed at each location. Specifically:

1. It is unclear what activities are performed at the (b) (4) site. Your firm's submission mentions that it is responsible for "GMP storage of finished product (b) (4) (b) (4) and prior to release and final packaging (storage only)". The receiving/final acceptance activities related to product stored at this site are unclear. Please explain how this site is related to your quality systems, and detail what acceptance activities are performed at (b) (4) versus at other facilities.
2. It is unclear what activities are performed at the (b) (4) site. Your firm's submission mentions that it is responsible for "(b) (4) (b) (4) of Polidocanol Injectable Microfoam Drug Product Fully Assembled Units (FAUs)". The receiving/final acceptance activities related to product (b) (4) at this facility are unclear. Please explain how this site is related to your quality systems, and detail what acceptance activities are performed at (b) (4) versus at other facilities.
3. It is unclear what activities are performed at the (b) (4) site. Your firm's submission mentions that it is responsible for "Storage of container closure components". It is unclear what components of the product are the "container closure components". Additionally, the receiving/final acceptance activities related to product stored at this site are unclear. Please explain how this site is related to your quality systems, and detail what acceptance activities are performed at (b) (4) versus at other facilities.

Please submit your response to your application by the close of business on **March 7, 2013**. Please provide to me a courtesy copy of your response.

Please acknowledge receipt of this message, and contact me if you have questions.

Sincerely,

Debbie Mesmer

Deborah Mesmer

Regulatory Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Division of New Drug Quality Assessment (DNDQA1)
Food and Drug Administration
White Oak Building 21, Rm 2623
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(301) 796-4023
deborah.mesmer@fda.hhs.gov

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/s/

DEBORAH M MESMER
03/06/2013

From: [Mesmer, Deborah](#)
To: ["Andreia Collier"](#)
Cc: [Monteleone, Michael V.](#)
Subject: NDA 205098 Information Request
Date: Monday, February 25, 2013 3:36:54 PM
Importance: High

Dear Ms. Collier,

Please refer to your submission dated February 12, 2013, received February 13, 2013.

Please indicate where in your application you have provided the contact information for **each** of the manufacturing sites. We find a contact person and their information listed only for the Biocompatibles UK Limited facility.

If this information has not been submitted to your NDA, please submit it prior to FDA close of business on **February 26, 2013**.

Please contact me if you have any questions.

Sincerely,

Debbie Mesmer

Deborah Mesmer

Regulatory Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Division of New Drug Quality Assessment (DNDQA1)
Food and Drug Administration
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(301) 796-4023
deborah.mesmer@fda.hhs.gov

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/s/

DEBORAH M MESMER
02/25/2013

From: [Mesmer, Deborah](#)
To: ["Andreia Collier"](#)
Cc: [Monteleone, Michael V.](#)
Subject: NDA 205098
Date: Monday, February 25, 2013 2:50:34 PM

Dear Ms. Collier,

Please refer to NDA 205098 dated February 1, 2013, received February 4, 2013, for Polidocanol Injectable Microfoam 1%.

We are conducting our filing review of your NDA. Please provide the following information by **February 28, 2013**:

1. The make, model, and serial number of the [REDACTED] (b) (4) of the final assembled units (FAU)
2. The location (room number) of the [REDACTED] (b) (4) manufacturing facility
3. The production cycle and validation cycle sterilization parameters (time and temperature)
4. The results of [REDACTED] (b) (4) indicator studies for the FAU sterilization validation cycles
5. Diagrams of [REDACTED] (b) (4) within the loads
6. The manufacturer, [REDACTED] (b) (4) indicators used for the cycles
7. The incubation parameters used for the biological indicators and the results of positive control studies
8. A statement as to whether or not the FAU will be reprocessed
9. The results of container closure integrity tests conducted on units exposed to the commercial sterilization cycles

Please acknowledge receipt of this message, and send to me a courtesy copy of your response.

Please contact me if you have any questions.

Sincerely,

Debbie Mesmer

Deborah Mesmer

Regulatory Project Manager for Quality

Office of New Drug Quality Assessment (ONDQA)

Division of New Drug Quality Assessment (DNDQA1)

Food and Drug Administration

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/s/

DEBORAH M MESMER
02/25/2013

RAMESH K SOOD
02/25/2013



NDA 205098

NDA ACKNOWLEDGMENT

Provensis Ltd
Attention: Andreia Collier
5 Fleet Place
London
EC4M 7RD
UK

Dear Ms. Collier:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: polidocanol injectable foam 1%

Date of Application: February 1, 2013

Date of Receipt: February 4, 2013

Our Reference Number: NDA 205098

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 5, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Cc:
BTG International Inc.
Attention: Heather McIntosh
US Agent for Provensis Ltd
Five Tower Bridge, Suite 800
300 Barr Harbor Drive
West Conshohocken, PA 19428-2998

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/s/

EDWARD J FROMM
02/13/2013

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2013. See instructions for OMB Statement, below.					
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET				
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm					
1. APPLICANT'S NAME AND ADDRESS PROVENSIS LTD Heather McIntosh 5 Fleet Place London EC4M 7RD GB	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 205-098				
2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE 610-943-3519	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:				
3. PRODUCT NAME Polidocanol Injectable Microfoam	6. USER FEE I.D. NUMBER PD3012830				
7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO PRIORITY REVIEW VOUCHER NUMBER:					
8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY					
9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO If a waiver has been granted, include a copy of the official FDA notification with your submission.					
OMB Statement: Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: <table style="width:100%; border: none;"> <tr> <td style="width: 33%; vertical-align: top;"> Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850 </td> <td style="width: 33%; vertical-align: top;"> Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850 </td> <td style="width: 33%; vertical-align: top;"> An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. </td> </tr> </table>			Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.			
PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE ANDREA COLLIER	TITLE VP, REGULATORY AFFAIRS	DATE 29 JAN / 2013			
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$1,958,800.00					
Form FDA 3397 (01/10)					