CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-159

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
22-159

NAME OF APPLICANT / NDA HOLDER
Novalar Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
OraVerse

ACTIVE INGREDIENT(S)	STRENGTH(S)
phentolamine mesylate	0.4 mg (0.235 mg/mL)

DOSAGE FORM
Injection, solution

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 only 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 file 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	b. Issue Date of Patent	c. Expiration Date of Patent
6,872,390	3/29/2005	5/11/2021

d. Name of Patent Owner
Novalar Pharmaceuticals, Inc.

Address *(of Patent Owner)*
12555 High Bluff Drive
Suite 300

City/State
San Diego, California

ZIP Code	FAX Number *(if available)*
92130	858-436-1101
Telephone Number	**E-Mail Address *(if available)***
858-436-1100	renteria@novalarpharm.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)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	**E-Mail Address *(if available)***

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ 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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 *(as listed in the patent)*	Does the patent claim 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 approved labeling.)*	

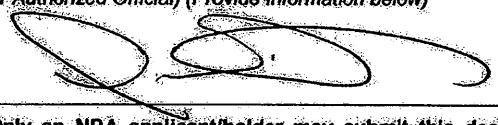
5. No Relevant Patents

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
	March 7, 2007

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.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Novalar Pharmaceuticals, Inc.	
Address 12555 High Bluff Drive Suite 300	City/State San Diego, California
ZIP Code 92130	Telephone Number 858-436-1130
FAX Number *(if available)* 858-436-1101	E-Mail Address *(if available)* navalta@novalarpharm.com

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
22-159

NAME OF APPLICANT / NDA HOLDER
Novalar Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
OraVerse

ACTIVE INGREDIENT(S)	STRENGTH(S)
phentolamine mesylate	0.4 mg (0.235 mg/mL)

DOSAGE FORM
Injection, solution

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 only 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 file 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	b. Issue Date of Patent	c. Expiration Date of Patent
6,764,678	7/20/2004	5/11/2021

d. Name of Patent Owner	Address *(of Patent Owner)*	
Novalar Pharmaceuticals, Inc.	12555 High Bluff Drive Suite 300	
	City/State San Diego, California	
	ZIP Code 92130	FAX Number *(if available)* 858-436-1101
	Telephone Number 858-436-1100	E-Mail Address *(if available)* renteria@novalarpharm.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)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ 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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 *(as listed in the patent)*: Claims 1-7, 12-16 — Does the patent claim 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 approved labeling.)* A method of reversing local anesthesia as described in Section 1-Indications and Usage in the proposed labeling.	

5. No Relevant Patents

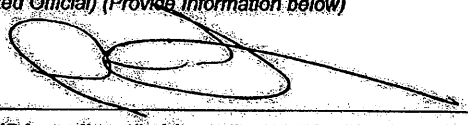
	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably 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: March 7, 2007

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.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Novalar Pharmaceuticals, Inc.

Address 12555 High Bluff Drive Suite 300	City/State San Diego, California
ZIP Code 92130	Telephone Number 858-436-1130
FAX Number *(if available)* 858-436-1101	E-Mail Address *(if available)* navalta@novalarpharm.com

1.3.5.2 Patent Certification

Paragraph I Certification for Regitine (phentolamine mesylate)

Regitine is listed in the FDA Orange Book as the reference listed drug (RLD) for phentolamine mesylate. Regitine® (NDA 8-278) marketed by Ciba (now Novartis)was approved in January 1952 for use in the diagnosis and treatment of patients with pheochromocytoma and for treatment and prevention of dermal necrosis following intravenous administration or extravasation of norepinephrine. Novalar's 505(b)(2) application intends to rely on the FDA's previous findings of safety for Regitine, as described in the Drug Efficacy Study Implementation (DESI) finding published in the Federal Register on April 6, 1971 (DESI 8278, Federal; Register Notice Volume 36, No. 66). Novartis discontinued marketing Regitine in the U.S. in 2000.

Patent Certification: "Paragraph I Certification": I, Novalar Pharmaceuticals, Inc. certify that patent information has not been submitted to the FDA for Regitine.

Donna Janson
President and Chief Executive Officer
Novalar Pharmaceuticals, Inc.

March 7, 2007
Date

EXCLUSIVITY SUMMARY

NDA # 22-159 SUPPL # HFD # 170

Trade Name OraVerse

Generic Name phentolamine mesylate injection

Applicant Name Novalar

Approval Date, If Known 5-9-08

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)(2)

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?

3 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# 40-235

NDA# 8-278

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:

NOVA 04-100, NOVA 04-200, NOVA-05-PEDS

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 X
Investigation #2	YES ☐	NO X
Investigation #3	YES ☐	NO X

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 X
Investigation #2	YES ☐	NO X

Investigation #3 YES ☐ NO X

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"):

NOVA 04-100, NOVA 04-200, NOVA-05-PEDS

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 # 65,095	YES X	! NO ☐
		! Explain:
Investigation #2		!
		!
IND # 65,095	YES X	! NO ☐
		! Explain:
Investigation #3		!
		!
IND # 65,095	YES X	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO X

If yes, explain:

Name of person completing form: Parinda Jani
Title: Chief, Project Management Staff
Date: 05-09-08

Name of Office/Division Director signing form: Rigoberto Roca, M.D.
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Parinda Jani
5/9/2008 04:55:57 PM

1.3.5.3 Exclusivity Request

In accordance with the provisions of 21 CFR 314.108 (b)(4), Novalar Pharmaceuticals, Inc. (Novalar) requests three years of exclusivity for the marketing of NV-101 (phentolamine mesylate) Injection for the indication for the reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor.

Regitine® is listed in the FDA Orange Book as the reference listed drug (RLD) for phentolamine mesylate. Regitine (NDA 8-278) was approved in January 1952 for and marketed by Ciba (now Novartis). Novalar's 505(b)(2) application intends to rely on the FDA's previous findings of safety and efficacy for Regitine, as described in the Drug Efficacy Study Implementation (DESI) finding published in the Federal Register on April 6, 1971 (DESI 8278, Federal Register Notice Volume 36, No. 66). Novartis discontinued marketing Regitine in the U.S. in 2000.

To the best of our knowledge, phentolamine mesylate has not been previously approved under section 505(b) of the act for the indication for the reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor. This NDA contains reports of new clinical investigations (in addition to Novalar sponsored bioavailability studies) conducted by Novalar that are essential to approval of the application.

This NDA includes the efficacy and safety results of 2 blinded, randomized, multicenter, phase 3 pivotal studies (NOVA 04-100 and NOVA 04-200) and a phase 2 study of pediatric patients (NOVA 05-PEDS) (of similar design) of NV-101 in dental patients with lingering STA due to receipt of an anesthetic containing a vasoconstrictor at the completion of routine dental and periodontal maintenance procedures (listed in Table 1).

All 3 studies demonstrated a significant reduction in the duration of STA as measured by lip palpation compared to the respective sham injection control groups ($p < 0.0001$). In both pivotal studies, the secondary endpoints, time to perception of normalcy (STAR-7 score of

zero), time to recovery of normal function (FAB), and time to recovery of normal sensation in the tongue (NOVA 04-100, mandibular study only) were all significantly reduced in the NV-101 group relative to the sham control group ($p < 0.0001$).

Table 1: Clinical Efficacy Studies with NV-101

Study ID	No. of Study Centers Locations	Status Total Enrollment/ Enrollment Goal	Study Design and Type of Control	Study Objective	Study & Ctrl Drugs Dose, Route & Regimen	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Median Age (Range)	Inclusion Criteria	Primary Endpoints
NOVA 04-100	18 U.S.	Completed 244/240	Blinded, randomized, controlled	Efficacy, safety	NV-101 0 (sham) 0.4 mg 0.8 mg Intraoral submucosal	 122/122 89/89 33/33	Single dose	120/124 32 (12-92)	Subjects (mandible) undergoing standard dental procedures	Time to recovery of normal sensation of the lower lip
NOVA 04-200	16 U.S.	Completed 240/240	Blinded, randomized, controlled	Efficacy, safety	NV-101 0 (sham) 0.4 mg 0.8 mg Intraoral submucosal	 120/120 113/113 7/7	Single dose	111/129 34 (12-81)	Subjects (maxilla) undergoing standard dental procedures	Time to recovery of normal sensation of the upper lip
NOVA 05-PEDS	11 U.S.	Completed 152/150	Blinded, randomized, controlled	Safety, efficacy	NV-101 0 (sham) 0.2 mg 0.4 mg Intraoral submucosal	 56/56 74/74 22/22	Single dose	75/77 8 (4-11)	Pediatric subjects aged 4 to 11 years undergoing standard dental procedures	Acceleration of the time to normal lip sensation in maxillary and mandibular procedures; for mandibular procedures, acceleration of time to normal tongue sensation

Study ID	No. of Study Centers Locations	Status Total Enrollment/ Enrollment Goal	Study Design and Type of Control	Study Objective	Study & Ctrl Drugs Dose, Route & Regimen	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Median Age (Range)	Inclusion Criteria	Primary Endpoints
NOVA 03-001	7 U.S.	Completed 122/120	Double-blind, randomized, placebo-controlled	Efficacy, safety	NV-101 0 (placebo) 0.4 mg 0.8 mg	 61/61 50/50 11/11	Single dose	54/68 23 (10-61)	Subjects undergoing standard dental procedures	Time to return to normal sensation in lips, tongue, nose, and chin
NOVA 02-01	1 U.S.	Completed 20/20	Double-blind, randomized, placebo-controlled	Safety, efficacy	Intraoral submucosal Phentolamine mesylate 0 (placebo) 0.2 mg	 10/10 10/10	Single dose	9/11 43 (27-50)	Healthy subjects	Time to return to normal sensation in lips, tongue, teeth, and chin
NOVA 02-02	1 U.S.	Completed 40/40	Dose-ranging, double-blind, randomized, placebo-controlled	Safety, efficacy	Intraoral submucosal Phentolamine mesylate 0 (placebo) 0.02 mg 0.06 mg 0.4 mg Intraoral submucosal	 10/10 10/10 10/10 10/10	Single dose	20/20 36 (19-60)	Healthy subjects	Time to return to normal sensation in lips, tongue, teeth, and chin

Study ID	No. of Study Centers Locations	Status Total Enrollment/ Enrollment Goal	Study Design and Type of Control	Study Objective	Study & Ctrl Drugs Dose, Route & Regimen	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Median Age (Range)	Inclusion Criteria	Primary Endpoints
NOVA 02-03	1 U.S.	Completed 32/32	Dose-ranging, double-blind, randomized, placebo-controlled	Safety, efficacy	Phentolamine mesylate 0 (placebo) 0.02 mg 0.08 mg 0.4 mg Intraoral submucosal	 9/9 8/8 7/7 8/8	Single dose	16/16 26 (18-48)	Healthy subjects	Time to return to normal sensation in upper lip, teeth, and nose

1.3.5.3.1 New Indication Certification

Novalar Pharmaceuticals, Inc. certifies as required by 21 CFR 314.54(a)(1)(iv) that the NV-101 (phentolamine mesylate) Injection NDA 505 (b) (2) application is for approval of a new indication, and not for the indications approved for the reference listed drug, Regitine®.

26 MAR 2007

Donna Janson
President and Chief Executive Officer
Novalar Pharmaceuticals, Inc.

Date

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-159 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: 4-9-07 **PDUFA Goal Date:** 5-9-08

HFD 170 **Trade and generic names/dosage form:** OraVerse (phentolamine mesylate) injection

Applicant: Novalar **Therapeutic Class:** 3S

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- X Yes. Please proceed to the next question.
- ☐ No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved:* for the prevention or control of hypertensive episodes that may occur in patients with pheochromocytoma, for the diagnosis of pheochromocytoma, and for the prevention or treatment of dermal necrosis and sloughing following IV administration or extravasation of norepinephrine.

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: ___ **for the reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor**

Is this an orphan indication?

- ☐ Yes. PREA does not apply. Skip to signature block.
- X No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- X No: Please check all that apply: X Partial Waiver X Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr.__0__ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__2__ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- X **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr.__2__ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__6__ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: Parinda Jani

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

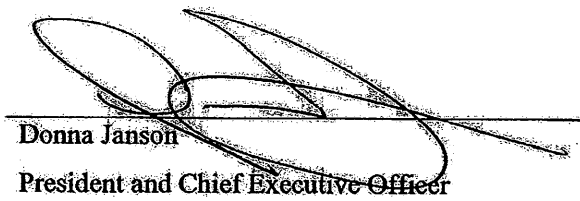
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dominic Chiapperino
5/8/2008 04:31:15 PM

1.3.3 Debarment Certification

Novalar Pharmaceuticals, Inc. certifies that we did not and will not use the services in any capacity, of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



March 7, 2007

Donna Janson
Date

President and Chief Executive Officer

Novalar Pharmaceuticals, Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
See Attached List for NV-101 Clinical Study Participating Investigators/Sub-Investigators	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
JENNIFER STANCIL	DIRECTOR OF FINANCE, CONTROLLER
FIRM / ORGANIZATION: NOVALAR PHARMACEUTICALS, INC.	
SIGNATURE: Jennifer D. Stancil	DATE: 3/7/07

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (4/06)

PSC Graphics (301) 443-1090 EF

4 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-159

Novalar Pharmaceuticals, Inc.
12555 High Bluff Drive, Suite 300
San Diego, CA 92130

Attention: Laura A. Navalta
Senior Vice President, Clinical and Regulatory

Dear Ms. Navalta:

Please refer to your April 9, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OraVerse (phentolamine mesylate).

On January 23, 2008, we received your major amendment to this application, containing new microbiology data and information. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 9, 2008.

If you have any questions, call Dominic Chiapperino, Regulatory Project Manager, at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Parinda Jani
1/29/2008 03:18:37 PM

Smith, Geri

From: Smith, Geri
Sent: Tuesday, October 16, 2007 5:02 PM
To: 'Laura Navalta'
Subject: Pharm Tox information request / NDA 22-159 / phentolamine

Hi Laura,

1. What does the abbreviation "N/D" stand for in the tables of section M3.2.P.2?

2. Please explain the denotation of "yes" in the isopropanol column of table 12 in section M3.2.P.2.4.1.

3. Is the [redacted] rubber used for the cap and plunger [redacted] used in any FDA-approved products currently on the market? b(4)

4. [redacted] has been shown to be extractable from the [redacted] rubber used for the cap and plunger (M3.2.P.2.4.1 table 11) in all three extraction conditions tested. No leachable assessment was performed. Based on the extraction data, exposure levels for [redacted] could potentially reach [redacted]. Provide a toxicological evaluation based on what is known from the literature to determine the safe level of exposure of [redacted] via the intended route of administration of your product.

Thanks,
Geri

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

/s/

Geraldine Smith
10/17/2007 10:00:44 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-159

INFORMATION REQUEST LETTER

Novalar Pharmaceuticals, Inc.
12555 High Bluff Drive, Suite 300
San Diego, CA 92130

Attention: Laura A. Navalta
Vice President of Clinical Operations

Dear Ms. Navalta:

Please refer to your April 9, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for phentolamine mesylate solution for injection, 0.4 mg (0.235 mg/mL).

We are reviewing the labeling section of your submission and have the following comments and information requests. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We request a prompt written response in order to continue our evaluation of your NDA.

PACKAGE INSERT

General

1. Capitalize the first letter of each key word in all subheadings.

2. Insert an additional "em" space between all heading/subheading numbers and their names.

3. Format all cross-references in the Full Prescribing Information section in the following manner: *[see Dosage and Administration (2.1)]*.

4. Avoid reporting percentages in decimals; use whole numbers.

Highlights

5. Revise the statement immediately following the drug names to read "solution for submucosal injection."

6. After "Initial U.S. Approval," replace "20XX" with "1952."

7. Under the INDICATIONS AND USAGE heading, add the pharmacologic class after "OraVerse is."

8. Under the INDICATIONS AND USAGE heading, add the major limitation that the drug is not to be used in children ages ——— b(4)

9. Under the DOSAGE AND ADMINISTRATION heading, use tabular format to enhance the accessibility of the information presented in the bulleted list.

10. Under the DOSAGE AND ADMINISTRATION heading, remove the extra "s" from "techniques(s)."

11. Under the DOSAGE FORMS AND STRENGTHS heading, insert "solution per" immediately before "cartridge."

12. Under the ADVERSE REACTIONS heading, insert Novalar's phone number.

13. Under the ADVERSE REACTIONS heading, insert the address of the Novalar web page dedicated to adverse reaction reporting.

14. Add the Patient Counseling Information Statement "See 17 for PATIENT COUNSELING INFORMATION."

15. After "Revised," replace "3/2007" with "MM/YYYY."

Contents

16. List all subsections included in the Full Prescribing Information. The number and name of each subsection should be listed under the name of the section of which it is a part.

17. Capitalize the first letter of the words "Full Prescribing Information" so that the footnote reads "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

Indications and Usage

18. Include the limitations for use in this section.

Dosage and Administration

19. In subsection "2.1 General Dosing Information," reformat the dosing scheme into tabular form.

20. In subsection "2.1 General Dosing Information," remove the extra "s" from "techniques(s)."

Dosage Forms and Strengths

21. Insert "solution per" immediately before "cartridge."

Warnings and Precautions

22. Move the information in subsection "5.2 Pregnancy" to the USE IN SPECIFIC POPULATIONS subsection "8.1 Pregnancy" since the drug is classified as Pregnancy Category C. Only drugs classified as Pregnancy Category D should contain pregnancy-related statements in the WARNINGS AND PRECAUTIONS section.

Adverse Reactions

23. Do not refer to adverse reactions as "adverse events."

Drug Interactions

24. Describe specific practical instructions for preventing or managing interactions.

25. Describe the mechanism of action of all drug interactions listed.

26. Add "(PK)" after the first appearance of "pharmacokinetic."

Use in Specific Populations

27. Insert into subsection "8.1 Pregnancy" the information that currently resides in the WARNINGS AND PRECAUTIONS subsection "5.2 Pregnancy."

Description

28. Include the pharmacologic or therapeutic class of the drug.

Clinical Studies

29. Delete the word " — " from the sentence containing "...were studied in the following pivotal clinical studies."

The Division of Medication Errors and Technical Support (DMETS), in the Office of Surveillance and Epidemiology (OSE), has the following comments regarding the proposed carton and container labels.

CONTAINER

30. Revise the statement regarding the product strength so that identification of the total milligrams per total volume is immediately followed by the milligram per milliliter concentration, as follows:

    0.4 mg/1.7 mL
    (0.23 mg/mL)

31. Relocate the product strength so that it immediately follows the proprietary and established names. In doing so, to avoid confusion, ensure that the product strength is not presented in close proximity to the net quantity.

32. Mark the cartridges with increments of measure to facilitate accurate administration of doses that consume less than one cartridge.

CARTON

33. Increase the font of the established name so that it is at least ½ the size of that of the proprietary name on both the 10-cartridge and the 50-cartridge cartons.

34. Revise the "Contents" statement to read "Contents: 50 Cartridges, 0.4 mg per 1.7 mL each" on the 50-cartridge carton.

Additionally, DMETS has not identified any objections to the use of your proposed proprietary name, OraVerse. This is considered a tentative decision that will be re-evaluated prior to the completion of our review.

If you have any questions, contact Geri Smith, Regulatory Project Manager, at geri.smith@fda.hhs.gov or (301) 796-2204.

Sincerely,

{See appended electronic signature page}

Sara Stradley
Chief, Project Management Staff
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Sara Stradley
10/10/2007 02:42:43 PM

Smith, Geri

From: Smith, Geri
Sent: Wednesday, October 03, 2007 11:51 AM
To: 'Laura Navalta'
Subject: NDA 22-159: CMC information requests

Attachments: Picture (Enhanced Metafile)

Hi Laura,

We have the following CMC information requests.

The proposed container closure system components are:

Component	Supplier	Composition	DMF Number
Dental Cartridge			
Plunger			
Cap			

b(4)

In addition, in the NDA it is mentioned in section 3.2.P.2.4.1 (where the extraction studies are described) that the extraction studies were performed on rubber stoppers.

1. Clarify whether the plunger and cap are coated with . If so, that should be specified in table 1 of section 3.2.P.7 and Table 1 of section 3.2.P.2.4. If not, why were the extraction studies (described in section 3.2.P.2.4.1) performed on rubber stoppers? b(4)

2. The Letter of Authorization for DMF fers only tc does not mention Please provide a revised Letter of Authorization including reference to (and reference to if applicable) along with reference to the location in the DMF (date of submission) where the information can be found and the record #.

Thanks,
Geri

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

/s/

Geraldine Smith
10/17/2007 09:59:09 AM
CSO

Smith, Geri

From: Smith, Geri
Sent: Monday, September 10, 2007 2:35 PM
To: 'Laura Navalta'
Subject: A few requests for NDA 22-159

Hi Laura,

Please provide the following to assist in our review of the subject NDA:

1. A list of all amendments to each of the clinical trials. Specify the trial name, the date of the amendment, and the specific changes made to the protocol.

2. A list of all protocol deviations for each of the two pivotal trials. Specify the trial name, the patient ID, date and time of the deviation, nature of the deviation, and how the deviation was dealt with.

Thanks,
Geri

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

/s/

Geraldine Smith
10/17/2007 09:57:12 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-159

Novalar Pharmaceuticals, Inc.
12555 High Bluff Drive, Suite 300
San Diego, CA 92130

Attention: Laura A. Navalta
Vice President of Clinical Operations

Dear Ms. Navalta:

Please refer to your April 9, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for phentolamine mesylate solution for injection, 0.4 mg (0.235 mg/mL).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on June 8, 2007, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, contact Geri Smith, Regulatory Project Manager, at geri.smith@fda.hhs.gov or (301) 796-2204.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Bob Rappaport
6/14/2007 08:46:21 PM

Smith, Geri

From: Smith, Geri
Sent: Tuesday, May 22, 2007 2:09 PM
To: 'Laura Navalta'
Subject: NDA 22-159: request from statistical reviewer

Hi Laura,

I owe you answers on a few outstanding items, which I'm working to get you. In the meantime, our statistical reviewer has requested that Novalar submit the following:

1. SAS programs for analysis (derived) data creation

2. SAS programs for efficacy analyses, including the subgroup analyses

3. SAS programs for safety analyses

Thanks!
Geri

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

/s/

Geraldine Smith
10/17/2007 09:54:44 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-159

NDA ACKNOWLEDGMENT

Novalar Pharmaceuticals, Inc.
12555 High Bluff Drive, Suite 300
San Diego, CA 92130

Attention: Laura A. Navalta
Vice President of Clinical Operations

Dear Ms. Navalta:

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

Name of Drug Product:	phentolamine mesylate solution for injection, 0.4 mg (0.235 mg/mL)
Review Priority Classification:	Standard (S)
Date of Application:	April 9, 2007
Date of Receipt:	April 9, 2007
Our Reference Number:	NDA 22-159

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 June 8, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 9, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have partially waived the pediatric study requirement for this application.

Please cite the NDA number listed above 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:

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

/s/

Geraldine Smith
4/27/2007 03:36:36 PM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	NDA 22-159
Drug Name:	OraVerse 0.4mg/1.7mL cartridge
Indication(s):	Proposed Indication: reversal of soft tissue anesthesia and associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor in [redacted] of age and older patients
Applicant:	Novalar Pharmaceuticals, Inc
Date(s):	Received 04/09/07; User Fee 02/09/08
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II/Office of Biostatistics
Statistical Reviewer:	Feng Zhou, M.S. (Statistical Reviewer)
Concurring Reviewers:	Dionne L. Price, Ph.D. (Statistical Team Leader)
Medical Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Clinical Team:	Arthur Simone, M.D. (Medical Reviewer)
Project Manager:	Geri Smith

b(4)

Keywords: NDA review, clinical studies

FILING CHECKLIST

Item	Check (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc.	Yes
Original protocols & subsequent amendments available in the NDA	Yes
Safety and efficacy for gender, racial, and geriatric subgroups investigated	Yes
Data sets in EDR conform to applicable guidance.	Yes

From a statistical perspective, the submission can be filed.

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-159 Supplement # n/a Efficacy Supplement Type SE- n/a

Proprietary Name: OraVerse (proposed)
Established Name: phentolamine mesylate
Strengths: 0.4 mg (0.235 mg/mL)

Applicant: Novalar Pharmaceuticals, Inc.
Agent for Applicant (if applicable): n/a

Date of Application: 09-Apr-07
Date of Receipt: 11-Apr-07
Date clock started after UN: n/a
Date of Filing Meeting: 21-May-07
Filing Date: 08-Jun-07
Action Goal Date (optional): 25-Jan-08 User Fee Goal Date: 09-Feb-08

Indication(s) requested: Reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor.

Type of Original NDA:	(b)(1) ☐	(b)(2) ☒
AND (if applicable)		
Type of Supplement:	(b)(1) ☐	(b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) n/a

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒

  If yes, explain:

  Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  n/a YES ☐ NO ☐
  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain: n/a

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain: (The submission contains the eCTD backbone and an HTML index.)

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☒
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 3 Years NO ☐
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ n/a ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? YES ☒ NO ☐
If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 65,095 (submitted 20-Jun-02)

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) 30-Oct-03 NO ☐
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 08-Dec-06 NO ☐
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) 26-Oct-05 NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

The 26-Oct-05 SPA GR letter pertained to the following two protocols:

NOVA 04-100 *A Phase 3, Multicenter, Randomized, Blinded, Controlled Study of NV-101 for Efficacy and Safety in Patients Undergoing Simple Mandibular Dental Procedures*

NOVA 04-200 *A Phase 3, Multicenter, Randomized, Blinded, Controlled Study of NV-101 for Efficacy and Safety in Patients Undergoing Simple Maxillary Dental Procedures*

Note: The Sponsor also submitted SPA requests for other protocols, for which agreements were apparently not reached, as summarized below.

On 6-Feb-04, the Division notified the Sponsor that its 19-Dec-03 SPA request was deficient. This request pertained to the following protocol:

NOVA 03-002 *A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study of the Effect of NV-101 on the Rate of Recovery from Soft-Tissue Anesthesia and on Safety in Dental Patients*

On 22-Feb-05, the Division recorded withdrawal of the Sponsor's 25-Jan-05 SPA request for a study in pediatric patients.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application: n/a

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? n/a YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team? YES ☒ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: 05-21-07

NDA #: 22-159

DRUG NAMES: OraVerse, NV-101, phentolamine mesylate, injection, 0.4 mg (0.235 mg/mL)

APPLICANT: Novalar Pharmaceuticals, Inc.

BACKGROUND: Novalar submitted this NDA under 505(b)(2) for OraVerse, proposing an indication of reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor. This application references Regitine (NDA 08-278).

ATTENDEES: Rigoberto Roca, Art Simone, Ali Al Hakim, Dan Mellon, Beth Bolan, Suresh Doddapaneni, David Lee, Tom Permutt, Geri Smith

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline/Organization	Reviewer
Medical:	Art Simone
Secondary Medical:	n/a
Statistical:	Feng Zhou
Pharmacology:	Beth Bolan
Statistical Pharmacology:	n/a
Chemistry:	Elsbeth Chikhale
Environmental Assessment (if needed):	n/a
Biopharmaceutical:	David Lee
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	n/a

DSI:
OPS:
Regulatory Project Management: Geri Smith
Other Consults: DMETS, DDMAC, SEALD, OSE, DSI, Micro

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☒

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☒ NO ☐
  If yes, was microbiology consulted for validation of sterilization?
  YES ☒ NO ☐

ELECTRONIC SUBMISSION:
Any comments: The submission is in eCTD format.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No issues have been identified.
- ☐ Issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Geri Smith
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
(3) 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) 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, and.

(3) **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) 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, or

(3) 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 Office of Regulatory Policy representative.**

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☒ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Regitine NDA 08-278

3. **Is this application for a drug that is an "old" antibiotic** (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
YES ☐ NO ☒

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?
YES ☐ NO ☒

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?
   YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Cited pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☒ NO ☐

The approved pharmaceutical alternatives are:

- NDA 08-278 / Regitine / phentolamine mesylate injection / Novartis
- NDA 40-235 / phentolamine mesylate injection / Bedford

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No,**" to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☒

According to COMIS, NDA 08-278 / Regitine injection was approved on 30-Jan-52 for the following indications:

- Prevention/control of hypertensive episodes with pheochromocytoma
- Prevention/treatment of dermal necrosis and sloughing after IV norepinephrine
- Diagnosis of pheochromocytoma

NDA 40-235 / phentolamine mesylate injection is approved as a generic version of Regitine.

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☒ NO ☐

NDA 08-278 (Regitine/phentolamine mesylate injection) is cited as the listed drug.

*If "**Yes,**" to (c), proceed to question 7.*

***NOTE:** If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No,**" to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☒ NO ☐

*If "**No,**" skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12. YES ☐ NO ☒

8. **Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").**

This application provides for a new indication entirely distinct from that of the listed drug.

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

11. Is the application for a duplicate of a listed drug whose only difference is **that the rate at which the product's active ingredient(s) is absorbed or made** available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) n/a YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☒ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s): Note: A search of patents on the U.S. Patent & Trademark Office web site did not identify any patents for Regitine.

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☒ NO ☐

*If "**Yes**," what is the listed drug product(s)?* Regitine

Which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug:

Primary Pharmacodynamics, Secondary Pharmacodynamics, Safety Pharmacology, Pharmacodynamic Drug Interactions, Pharmacokinetics, Single-Dose Toxicology, Repeat-Dose Toxicology, Carcinogenicity, and Reproductive and Developmental Toxicology. See the table below for corresponding eCTD numbers.

		Source	
eCTD section	***Nonclinical Studies***	***Sponsor's data***	***Agency's previous findings for Regitine® and/or published literature***
4.2.1.1	Primary Pharmacodynamics	X	X
4.2.1.2	Secondary Pharmacodynamics	X	X
4.2.1.3	Safety Pharmacology		X
4.2.1.4	Pharmacodynamic Drug Interactions		X
4.2.2	Pharmacokinetics		X
4.2.3.1	Single-Dose Toxicology	X	X
4.2.3.2	Repeat-Dose Toxicology		X
4.2.3.3	Genotoxicity	X	
4.2.3.4	Carcinogenicity		X
4.2.3.5	Reproductive and Developmental Toxicology	X	X
4.2.3.6	Local Tolerance	X	

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☒ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☒ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☒

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Geraldine Smith
11/2/2007 08:22:28 AM
CSO

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

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 CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

NOVALAR PHARMACEUTICALS INC
Laura Navalta
12555 HIGH BLUFF DR SUITE 300
SanDiego Ca 92130
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22-159

2. TELEPHONE NUMBER
858-4361130

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] 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:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
phentolamine mesylate

6. USER FEE I.D. NUMBER
PD3007178

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, 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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	President + CEO	March 16, 2007

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$896,200.00

Form FDA 3397 (12/03)

Close Print Cover sheet

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,095

Novalar Pharmaceuticals, Inc.
12555 High Bluff Drive, Suite 300
San Diego, CA 92130

Attention: Laura A. Navalta
Vice President of Clinical Operations

Dear Ms. Navalta:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NV-101 (phentolamine mesylate) injection for the reversal of soft tissue anesthesia and the associated functional deficits resulting from intraoral injection of local anesthetic containing a vasoconstrictor.

We also refer to the meeting between representatives of your firm and the FDA on December 8, 2006. The purpose of the meeting was to discuss topics relating to your New Drug Application (NDA) submission planned for April 2007, such as the efficacy and safety data from the studies that will serve as the basis for your NDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact me at geri.smith@fda.hhs.gov or (301) 796-2204.

Sincerely,

{See appended electronic signature page}

Geri Smith
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 8, 2006

TIME: 2:30 PM – 4:00 PM

LOCATION: White Oak Building 22, Conference Room 1311
10903 New Hampshire Avenue, Silver Spring, MD 20993

APPLICATION: IND 65,095

PRODUCT: NV-101 (phentolamine mesylate) for injection

INDICATION: Reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral injection of a local anesthetic containing a vasoconstrictor

SPONSOR: Novalar Pharmaceuticals, Inc. ("Novalar")

TYPE OF MEETING: Pre-NDA (Type B)

MEETING CHAIR: Sharon H. Hertz, M.D., Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

MEETING RECORDER: Geri Smith, Regulatory Project Manager

FDA Attendees	Title
Bob Rappaport, M.D.	Director, DAARP
Sharon H. Hertz, M.D.	Deputy Director/Medical Team Leader
Arthur Simone, M.D., Ph.D.	Medical Officer
Dan Mellon, Ph.D.	Supervisory Pharmacologist/Toxicologist
Elizabeth Bolan, Ph.D.	Pharmacology/Toxicology Reviewer
Ravi Harapanhalli, Ph.D.	Chief, CMC Branch V, Division of Pre-Marketing Assessment III & Manufacturing Science
Ali Al Hakim, Ph.D.	Pharmaceutical Assessment Leader (PAL)
Geri Smith	Regulatory Project Manager
Novalar Attendees	**Title**
Donna Janson	President and CEO
Laura A. Navalta	Vice President, Clinical Operations
Bruce Rutherford, D.D.S., Ph.D.	Vice President, Clinical Development and Medical Monitor
	CMC Consultant
	Biostatistics Consultant
	Regulatory Consultant
	Nonclinical Consultant

b(4)

BACKGROUND

The Sponsor requested this Pre-NDA meeting to discuss topics relating to its NDA submission planned for April 2007, such as the adequacy of the efficacy and safety data from the studies that will serve as the basis for the NDA. Each of the Sponsor's questions is presented below in italics, followed by the Division's response in bold. A record of the discussion that occurred during the meeting is presented in normal font. The Division provided written responses to the Sponsor on December 7, 2006. The Sponsor requested that the meeting focus on Questions 7, 10 and 8, Additional CMC Comments 3, 5e, 5f, 6c, 6d and 6e, and Question 14, in that order.

DISCUSSION OF QUESTIONS

Question 1

Drug substance for the commercial product will continue to be supplied by ——— . ———————) under Drug Master File (DMF) No. —— In addition to the tests required by the United States Pharmacopoeia (USP) monograph and reported in ——— certificates of analysis, Novalar will perform high performance liquid chromatography (HPLC) purity, endotoxins, and bioburden on incoming drug substance as confirmatory testing. Novalar proposes to perform full USP and additional tests on the —— batches per year; subsequent batches will be tested for confirmatory identification as well as the Novalar tests for HPLC purity, endotoxins, and bioburden. Does the Division agree with this proposal? b(4)

FDA Response

The proposal is acceptable provided that:

1. **The Drug Master File remains adequate to support the use of the Active Pharmaceutical Ingredient (API).**
2. **Test results from the above ——batches remain within the approved specifications.** b(4)
3. **Data from all batches are provided in the annual report of the NDA.**

Discussion

This question was not discussed at the meeting.

Question 2

Pursuant to the request by the Division at the end of phase 2 (EOP2) meeting, Novalar has performed analysis for the possible presence of ——————— ; in the drug substance using a validated gas chromatography-mass spectroscopy (GC-MS) procedure. A total of 6 batches of ——— drug substance have been tested with a result of "none detected" in each of the 6 batches. Novalar believes that this is sufficient to demonstrate the absence of these b(4)

potential process impurities in the drug substance and that no further testing is required. Does the Division agree with this proposal?

FDA Response

The proposal is acceptable. However, in order to confirm the absence of these potentially genotoxic materials, provide a detailed description of the gas chromatography method together with the corresponding test results and limits of detection. Any additional manufacturing/processing changes that may result in the introduction of [redacted] into the drug substance and into the drug product should be reevaluated for these genotoxic impurities and reported to the agency.

Discussion

This question was not discussed at the meeting.

Question 3

A comparison of the NDA-registration and proposed commercial drug product specifications will be provided. Based on the results of the NDA-registration stability lots at release and throughout stability, Novalar proposes to eliminate [redacted] b(4)

[redacted] ıg), and to specify separate release and stability acceptance criteria for assay and related substances. The Division's comments regarding the proposed commercial specification are sought.

FDA Response

Provide an explanation for the variation in the results from the cartridge integrity test and state clearly whether the variation was due to laboratory error and/or lapses in manufacturing controls. The acceptability of eliminating the above tests from the drug product specifications will depend on a full understanding of this variation and how it is controlled. Also, provide the details of the test method and acceptance criteria used for this test, and the test results (release and stability) for all registration batches in the NDA.

Discussion

This question was not discussed at the meeting.

Question 4

Pursuant to the proposed changes in the commercial specification, Novalar proposes to [redacted] b(4)

dose from the commercial drug product stability protocols. Does the Division agree with this proposal?

FDA Response

A satisfactory response to Question 3 is needed before this can be addressed.

Discussion

This question was not discussed at the meeting.

Question 5

Novalar plans to include — onths of stability data on the 3 NDA-registration stability lots of the NV-101 drug product and request a 36-month expiry that will be limited for the most part by the levels of the 2 major related substances. The Division's comments regarding the proposed expiry are sought.

FDA Response

The expiry dating for the drug product will be based on the quality of the real-time stability test data, including the level of related substances and degradation products, and the extent to which they are considered qualified in the preclinical safety studies. Provide stability data in SAS transport format and statistical analysis of all stability-indicating quality attributes for the registration batches.

Discussion

This question was not discussed at the meeting.

Question 6

Based on recent guidance from the Agency, Novalar plans to file the executed batch records for the 3 NDA-registration stability lots and the current (phase 3) clinical lot of the NV-101 drug product in the NDA. Novalar does not plan to file the commercial batch record, relying instead on the detailed description of the manufacturing process, or the executed batch record for the phase 2 lot of product that was manufactured at [redacted]) at [redacted] Does the Division agree with this proposal? b(4)

FDA Response

We interpret this question to mean that the executed batch records for the batches used in the Phase 3 and NDA stability studies would be submitted in the NDA. That is acceptable provided that an adequate and appropriate description of the commercial manufacturing process is provided in the NDA and is represented by the executed batch records used in Phase 3 studies.

Successful process validation is required before commercial marketing of the product. Therefore, you should discuss your approach to process validation with the district office.

Discussion

This question was not discussed at the meeting.

Question 7

Novalar hopes to be able to provide the previously requested samples of NV-101 cartridges proposed for commercial distribution (i.e., [redacted] A sampling of commercial dental anesthetic products will also be provided as comparator samples. If these samples are made available for review about 1 month prior to this meeting, Novalar requests comments from the Division of Medical Errors regarding the adequacy of the design at the meeting. If the samples are available in a timely fashion, does the Agency concur with the design proposal?

b(4)

FDA Response

The Division of Medication Errors and Technical Support (DMETS) is currently reviewing the samples submitted on November 7, 2006, in response to the Division's July 19, 2006, request. The Division will forward comments from DMETS under separate cover. However, product samples should also be submitted for the CMC review of the NDA.

Discussion

The Sponsor inquired as to when the Division would provide comments from DMETS, and whether DMETS or the Division was the final authority regarding the acceptability of the proposed packaging. The Sponsor explained that, once the packaging is found acceptable to the Agency, it will take [redacted] after ordering the packaging equipment for the equipment to be qualified for production use. If the Agency finds the proposed packaging unacceptable, then significantly more time may be needed for the Sponsor to find an alternative.

b(4)

The Division stated that it expects comments from DMETS in approximately one month, and that DMETS is an advisor to the Division. Thus, the Division will make the final determination regarding the acceptability of the packaging after considering comments from other relevant divisions, such as DMETS. The Division explained that it has concerns for patient safety based on the potential for clinicians to confuse this product with marketed anesthetics. The Division stated that it is important that NV-101 be readily discernable from other products when the cartridges are inside the blister packs, separated from the blister packs, and mounted in syringes.

The Division stated that this is the first time DMETS is commenting on the NV-101 packaging and, as such, the Sponsor should anticipate that DMETS will have several recommendations. The Division clarified that sponsors typically first receive DMETS comments on proposed packaging during the Agency's review of a submitted NDA, thus the Sponsor will receive comments from DMETS earlier than usual for NV-101. The Division stated that it could not commit to provide comments to the Sponsor by a specific date.

The Sponsor explained that the product is packaged in a standard dental cartridge and that neither the cartridge nor the injector is unique to NV-101. The Sponsor proposed to differentiate this product through its labeling background—the NV-101 label has a —— background to distinguish it from anesthetic labels, which have a —— background. b(4)

The Division expressed concern that the blue ferrule on the cartridge is not visible when the cartridge is inserted into a dental syringe. The Sponsor stated that it could use a blue plunger to distinguish the product from dental anesthetics, and provide bridging data to demonstrate that the change in color of the plunger does not introduce issues. The Division stated that, if the Sponsor distinguishes this product with a method that does not contact the product, far less data will be required to show that product integrity is preserved. The Sponsor stated that it originally applied a —————————— to the cartridge and did not apply a band of color, specifically to distinguish the product from dental anesthetics. The Division stated that this marking scheme may not easily carry over to future generic products and/or other like products that may enter the market. The Division pointed out that there is available space above the blue band that could be used for distinguishing graphics, possibly through the use of a hologram or etched glass. The Division clarified that if the Sponsor chose to add a hologram or to etch the glass, the Sponsor could either ensure that the glass manufacturer's drug master file (DMF) was updated with this information, or the Sponsor could include this information in Module 3 of the NDA. b(4)

The Sponsor decided against another option—————————— —out of concern that —— would hinder attempts by the clinician to detect particulates and impurities in the solution before administration. The Sponsor agreed to consider the Division's comments with regard to ensuring that NV-101 is distinguishable from dental anesthetics. b(4)

The Division stated that it understands that the risks associated with confusion of NV-101 with local anesthetics are likely to be non-life-threatening and only mild to moderate in nature, and that the severity of the risk would determine the extent to which NV-101 would have to be made discernible from other injectable dental products.

The Sponsor requested clarification regarding what samples must be submitted with the NDA. The Sponsor planned to submit photographs/diagrams of the proposed draft labels, immediate container and secondary packaging in an electronic eCTD NDA. The Sponsor had not planned to submit physical samples of the product, but offered to provide mock-

ups of the product if necessary. The Division requested that the Sponsor submit physical samples of the product directly to the project manager upon submission of the electronic NDA. At the conclusion of the meeting, the Sponsor provided the Division with samples of the current NV-101 cartridges, four different dental local anesthetics in blister packaging, and a syringe. Thus, the Division agreed that the Sponsor would only need to provide NV-101 cartridges in blister packaging at the time of NDA submission.

The Division advised the Sponsor to ensure that data for the extractables and leachables are included in the NDA. The Sponsor should also include the specifications for — of the product, including the amount — that breaks loose, which may affect the syringeability of the cartridges. Additionally, the Sponsor agreed to provide a summary of product quality issues/complaints that were identified during clinical trials. b(4)

Question 8

In support of process validation, assurance of sterility for the Novocol manufacturing process, Novalar plans to include information and data including results from sterilizing-filter integrity studies, media fill specifications, procedures, results, and action for failures, environmental monitoring methods and exceed limits, sterility and endotoxin test procedures and validation data summaries, detailed summaries of sterilization and — studies for manufacturing equipment and container-closure components, floor plans of the Novocol facilities, and evidence of formal written procedures (a relevant SOP list). Are there other types of information or data summaries that the Division would prefer be included in this section of the NDA? b(4)

FDA Response

The information should be provided in the microbiological section of the NDA.

Discussion

The Sponsor inquired as to what additional types of information or data summaries should be included in this section of the NDA. The Division advised the Sponsor to follow these guidances on sterilization to avoid filing issues: — b(4)

Question 9

Novalar plans to request a waiver from the requirement to prepare an Environmental Assessment in support of the NDA since the amount of drug substance required for commercial distribution will be less than — based on current marketing estimates. This results in an estimated introductory concentration (EIC) far below the threshold of 1 ppm. To the best of b(4)

Novalar's knowledge, no extraordinary circumstances exist. Does the Division agree with this approach?

FDA Response

Provide the calculations with the request for a waiver in the NDA. Note that categorical exclusion from the requirement to prepare an Environmental Assessment (EA) should be supported by an EIC of 1 PPB or less. Refer to the July 1998 Agency guidance entitled "Environmental Assessment of Human Drug and Biologics Applications."

Discussion

This question was not discussed at the meeting.

Question 10

Based on the feedback at the EOP2 meeting, Novalar has completed or purchased the following toxicology studies with phentolamine: 1) a single dose, local tolerance study in the dog, including histological analysis of neurological tissues, 2) a standard battery of genotoxicity studies, 3) genotoxicity and dog toxicity studies to qualify the — impurities/degradation products [redacted] and 4) a male fertility study. Novalar plans to also provide a detailed literature review of phentolamine pharmacology, pharmacokinetic, and toxicology. Does the Division concur that a review of the literature on the nonclinical pharmacology, pharmacokinetics, and toxicology in addition to the toxicology studies referenced above is acceptable for fulfilling the requirements of the Nonclinical Pharmacology and Toxicology Sections of the NDA? b(4)

FDA Response

The phentolamine mesylate degradation product [redacted] yielded a positive result in the *in vitro* Mammalian Chromosome Aberration Test (Study No. —). To further assess the clastogenic potential of [redacted] evaluate the degradant at the maximum tolerated dose in an *in vivo* Micronucleus Test. In the event of a positive result, a carcinogenicity evaluation demonstrating a negative result will be necessary or human exposure must be limited to a total daily intake of [redacted] Note that this level represents the Agency's current thinking on this topic which is subject to change based on evolving scientific and regulatory considerations. b(4)

The adequacy of the toxicity studies and nonclinical literature review can only be determined upon evaluation of the NDA. Please include copies of all cited literature in your NDA submission.

Discussion

Responding to the Division's concern about the toxicity of the degradant, [redacted] the Sponsor stated that there is a high rate of cell change in studies such as these; b(4)

historical controls often change greatly, and 30-50% of chromosome aberration studies show positive results. The Sponsor believes that a fluke in the conditions of the study caused the positive result because no osmotic differences were found. The Sponsor considers the results of this study to be within normal limits and biologically insignificant, and does not believe that the results should cause concern.

The Division responded that the *in-vitro* chromosome aberration test is accepted by the International Conference on Harmonization (ICH) as a valid assay. The Division's review included consultation with Dr. David Jacobson-Kram, Associate Director of Pharmacology/Toxicology and an expert in this field, who agreed that the study showed a positive result. The Division stated that, in this situation, it recommends a third study, preferably an *in-vivo* micronucleus test, be conducted because the positive result in the chromosome aberration test is a signal that requires further evaluation. This approach is consistent with the document *Guidance for Industry and Review Staff: Recommended Approaches to Integration of Genetic Toxicology Study Results*. The Division explained that a third study producing negative results should help alleviate the Division's concern.

The Sponsor asked whether the third *in-vivo* study could be submitted after the NDA is submitted. The Division responded that the NDA must be complete at the time of submission. Material that is submitted after the NDA submission might not be reviewed during the review cycle, based on time constraints, and this would create problems if that material is critical to the application.

The Sponsor inquired as to whether an *in-vitro* chromosomal aberration assay using human lymphocytes could be performed *in lieu* of an *in-vivo* micronucleus test. The Division responded that this would be acceptable; however, the Sponsor should justify the rationale for use of that assay. The Division will fully evaluate the results of the assay upon submission of the NDA. Ultimately, it is the Sponsor's responsibility to demonstrate that this positive test result is not a concern. If the Sponsor fails to do so, human exposure must be limited to a total daily intake of —— . b(4)

The Sponsor requested clarification of the origin of the —— level proposed. The Division referred the Sponsor to the European Medical Agency's (EMEA) Committee for Medicinal Products for Human Use (CHMP) guidance entitled *Guideline on the Limits of Genotoxic Impurities*. The Agency is in the final stages of drafting a guidance document on this subject, however, the —— lay level represents the Division's current thinking on the topic. The Division reiterated that —— efers to a maximum daily intake.

The Sponsor stated that it is extrapolating a three-month shelf life from the studies. The Sponsor is in communication with the packager, Novocol, regarding the method of sterilization. Novocol prefers ——————————— ., however, b(4)
——————————— ıe Sponsor has data for modified formulations of different pH levels. In small-scale studies, these
——————————— le
———————————

Question 11

Novalar believes that the statistically significant differences (p <0.0001) in the primary efficacy endpoint of time to normal lip sensation between NV-101 and sham (control) in dental subjects from the two phase 3 studies, NOVA 04-100 and NOVA 04-200, supported by statistically significant differences (p <0.0001) in all of the secondary endpoints, demonstrates evidence of effect of NV-101 to reverse soft tissue anesthesia and the associated functional deficits caused by local anesthetics containing a vasoconstrictor using intraoral injection techniques. Does the Division consider the efficacy endpoints reached in these studies adequate demonstration of the efficacy of NV-101 to support filing an NDA?

FDA Response

These were the endpoints that were discussed and agreed upon at previous meetings and it appears, on preliminary review, that the two trials are adequate and well-controlled as designed and conducted.

Discussion

This question was not discussed at the meeting.

Question 12

Pediatric (children and adolescents), adult, and geriatric subjects were enrolled into the clinical study program. Additionally, four different anesthetics were included in the clinical study program: 1) 2% lidocaine with 1:100,000 epinephrine 2) 4% articaine with 1:100,000 epinephrine, 3) 4% prilocaine with 1:200,000 epinephrine, and 4) 2% mepivacaine with 1:20,000 levonordefrin. Finally, subjects could receive either 1/2, 1, or 2 cartridges (and therefore 1/2, 1, or 2 injections) of anesthetic, administered by 1 of the following intraoral injection techniques: 1) inferior alveolar nerve block, 2) Gow-Gates nerve block, 3) Vazirani-Akinosi block, 4) mental-incisive block or 5) supraperiosteal injection. Novalar believes that sufficient numbers of subjects were enrolled and treated in each of the demographic groups using the several different anesthetics and several different injection techniques. Does the Division agree that the population studied is adequate to support the following indication: NV-101 is indicated for the reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral injection of a local anesthetic containing a vasoconstrictor?

FDA Response

Your proposed program appears adequate to support the proposed indication as long as the distribution of patients and anesthetics permits evaluation of the relevant conditions of use.

Discussion

This question was not discussed at the meeting.

Question 13

For the Integrated Summary of Efficacy (ISE), Novalar proposes presenting studies together in 2 separate groups.

The first group is the 3 studies in which these efficacy data were collected in a well-controlled, multi-center, comparator arm fashion using a sham injection control group (NOVA 04-100, NOVA 04-200, and NOVA 05-PEDS). Detailed descriptions of these studies may be found in Section 9.5.

The second group is the 4 studies that used phentolamine mesylate (NOVA 02-01, NOVA 02-02, NOVA 02-03, and NOVA 03-001). Summaries of these studies may be found in Section 9.

For each group results will be presented in a single table comparing the results side-by-side. Does the Division agree with this approach?

FDA Response

This is acceptable.

Discussion

This question was not discussed at the meeting.

Question 14

For the Integrated Summary of Safety (ISS), Novalar proposes pooling studies based on whether dental procedures (dental subjects) or not (healthy volunteers) were performed on the subjects receiving study drug or control and safety data was collected. The 4 studies where dental procedures were not performed, but safety data were collected are NOVA 02-01, NOVA 02-02, NOVA 02-03, and NOVA 04-PK. The 5 studies where dental procedures were performed after administration of NV-101 or control and safety data were collected are NOVA 03-001, NOVA 05-PEDS-PK, NOVA 05-PEDS, NOVA 04-100, and NOVA 04-200. A table of contents of the ISS is appended as Attachment 4. Please note the studies in which [redacted] as not administered, will not be included in the ISS. Does the Division concur with this pooling strategy and studies planned to be included in the ISS? b(4)

FDA Response

This is acceptable. In addition, safety should be compared based on treatment (sham, vehicle, and dose of phentolamine) and for use both with and without dental procedures.

Discussion

The Sponsor proposed modifying the pooling strategy outlined in this question to remove study *NOVA 04-PK* from the pool of the four studies (*NOVA 02-01, NOVA 02-02, NOVA 02-03, and NOVA 04-PK*) where dental procedures were not performed, although study *NOVA 04-PK* would still be submitted with the NDA. The Sponsor explained that there would be three pools—one including the five studies involving dental procedures, one including the three studies of healthy subjects, and one including study *NOVA 04-PK*. The Division concurred with this plan.

Question 15

Novalar is planning to submit an ISE that is identical to Module 2.7.3 Summary of Efficacy. Does the Division agree this is acceptable?

FDA Response

This is acceptable provided the submission is consistent with the guidelines for an eCTD.

Discussion

This question was not discussed at the meeting.

Question 16

At the EOP2 meeting on October 30, 2003, the Division stated that information from the Description, Contraindications, Warnings, Precautions, and Adverse Reactions section of the current phentolamine label will likely carry over to the NV-101 label. Novalar has reviewed these sections and believes that certain statements currently contained are not relevant for inclusion in prescribing information for NV-101. While not an exhaustive list, there are 2 paragraphs below, 1 from Contraindications and 1 from Warnings that Novalar believes are not relevant to NV-101 and are not planned for inclusion in the NV-101 prescribing information. Does the Division agree with this plan?

Two paragraphs not planned to be included in the NV-101 prescribing information:

b(4)

b(4)

FDA Response

The labeling will be reviewed during the review cycle.

Discussion

This question was not discussed at the meeting.

Question 17

Novalar had planned to submit case report forms (CRFs) for subjects that either died while on study or within 28 days of treatment, experienced a serious adverse event, or withdrew due to an adverse event. Currently, all clinical studies have completed dosing subjects and no additional studies are planned at this time, and for the NV-101 clinical program no subjects died while on study, experienced a serious adverse event, or withdrew from study participation due to an adverse event. Therefore, Novalar does not plan to submit any CRFs in the NDA. Does the Division concur with this plan?

FDA Response

This is consistent with the regulations and, therefore, is acceptable. A statement of these findings should be included in the appropriate sections of the eCTD.

Discussion

This question was not discussed at the meeting.

Question 18

Novalar had planned to submit patient narratives for those subjects that died while on study, experienced a serious adverse event, or withdrew from study participation. Currently, all clinical studies have completed dosing subjects and no additional studies are planned at this time, and for the NV-101 clinical program no subjects died while on study, experienced a serious adverse event, or withdrew from study participation due to an adverse event. Therefore, Novalar does not plan to submit any patient narratives in the NDA. Does the Division concur with this plan?

FDA Response

This is consistent with the regulations and, therefore, is acceptable. A statement of these findings should be included in the appropriate sections of the eCTD.

Discussion

This question was not discussed at the meeting.

Question 19

Novalar conducted two pharmacokinetic (PK) studies, one in pediatric subjects (NOVA 05-PEDS-PK) and one in adult healthy subjects (NOVA 04-PK). Additionally, Novalar characterized the pharmacodynamics of NV-101 in NOVA 04-100 and NOVA 04-200 and the drug interaction of NV-101 and lidocaine in NOVA 04-PK. Novalar believes the clinical pharmacokinetics and pharmacodynamics of NV-101 have been adequately characterized in the aforementioned studies. The data from these studies in addition to a comprehensive literature review will be included in the NDA. Does the Division consider this sufficient to support the clinical pharmacology section of the NV-101 NDA?

FDA Response

Yes.

Discussion

This question was not discussed at the meeting.

Question 20

Novalar will submit datasets for all studies in SAS System XPORT transport format following the most recent FDA guidelines (Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, April 2006). Is the Division aware of any changes in Agency requirements that may occur prior to the planned submission date of April 2007?

FDA Response

The referenced guidance document provides the most current advice.

Discussion

This question was not discussed at the meeting.

Question 21

At the Type A meeting on November 18, 2004, the Division indicated that it expects to have NV-101 presented to the FDA Advisory Committee prior to the Division taking an action on the NDA. Can the Division provide an update on whether this is still planned?

FDA Response

The development and validation of the STAR questionnaire and the FAB tests have allowed an assessment of the clinical utility of NV-101. Provided the data support the validation process and a finding of efficacy, and the safety profile indicates a very small risk, there is not likely to be a need for an Advisory Committee meeting.

Discussion

This question was not discussed at the meeting.

Question 22

The clinical development program for NV-101 includes pediatric subjects 3 years through 18 years. Novalar plans to submit a partial pediatric waiver request pursuant to the Pediatric Research Equity Act (PREA) for pediatrics 0-2 years of age. Does the Division concur with this plan?

FDA Response

Justification for granting a waiver should be included in the NDA.

Discussion

This question was not discussed at the meeting.

Question 23

The NDA will be submitted in eCTD format following the most recent FDA guidelines for submitting NDAs in eCTD format. Novalar is working with [redacted] *to assure that the submission meets all eCTD requirements. The eCTD will be submitted through the electronic submission gateway (ESG) by* [redacted] *on behalf of Novalar. Are there any special requests the Division has for this submission? Additionally, does the Division agree that the review and archival copy of the NDA may also be provided in electronic format?*

b(4)

FDA Response

The Division has no special requests related to the electronic submission of this NDA. There is no need to provide separate archival and review copies of the NDA if the NDA is submitted in eCTD format through the ESG.

Discussion

This question was not discussed at the meeting.

Question 24

Since results from the two phase 3 studies, NOVA 04-100 and NOVA 04-200, demonstrated statistically significant differences (p <0.0001) in secondary endpoints, FAB and STAR-7, Novalar proposes that the FAB results be used to justify the proposed indication:

[redacted] b(4)

Further, Novalar proposes the clinical studies section of the prescribing information include the following details on the FAB and STAR:

[redacted] b(4)

The Division's feedback is requested on this proposed wording at the meeting.

FDA Response

We can not discuss the exact wording of the label until we have reviewed the studies and their results following filing of the NDA. As such, discussion regarding the wording of the label will take place toward the end of the NDA review period.

Discussion

This question was not discussed at the meeting.

Additional CMC Comments for the Proposed NDA

1. **Ensure that all facilities are listed as being ready for inspection on the day the application is submitted, and include a statement attesting to this in the NDA cover letter.**

   Discussion

   This comment was not discussed at the meeting.

2. **In the administrative section of the NDA, include a table of all facilities, their addresses, their roles and the names of the responsible personnel.**

   Discussion

   This comment was not discussed at the meeting.

3. **Provide a well-documented Pharmaceutical Development Report highlighting the critical quality attributes and critical process parameters, formulation development, design of experiments, and applicable quality-by-design elements. Refer to the ICH-Q8 guideline entitled "Pharmaceutical Development."**

   Discussion

   The Sponsor stated that this presentation is the only product/package that Novocol makes. The only deviation from Novocol's standard presentation for the NV-101 product is the color of the line seal and the formulation of the rubber. The Sponsor requested clarification regarding whether it should submit Novocol's Pharmaceutical Development Report for this presentation.

   The Division advised the Sponsor that a summary of the data would be acceptable for the report if it includes the appropriate links to the actual data. The Sponsor stated that it could write this report specifically about the NV-101 product, rather than submitting Novocol's general report. The Division agreed with this approach, and reminded the Sponsor to include the information along with other developmental information as recommended in the ICH guideline *ICH Q8*.

4. **Any stability updates should be submitted by the mid-cycle of the review for a timely assessment.**

   Discussion

   This comment was not discussed at the meeting.

5. **Adequate manufacturing and packaging controls should be in place to minimize the following product quality issues:**

    a. **Missing, leaking, or damaged tip caps.**

    b. **Tip caps falling off in packaging.**

    c. **Cracked cartridges.**

    d. **Damaged immediate cartons.**

    e. **Leaking cartridges upon receipt by the customers.**

    f. **Cartridges cracking during use.**

    g. **Missing components.**

    h. **Defective backer plates.**

    i. **Sticking or hard-to-push plungers.**

    j. **Empty cartridges.**

Discussion

The Sponsor requested clarification of how the Division expects the Sponsor to implement controls to minimize leaking cartridges upon receipt by customers. The Division advised the Sponsor to design the manufacturing specifications and sampling and testing strategies to avoid the potential for cartridges to leak before they reach the customer. The Division clarified that it intended the above list to be exhaustive, and that only the quality issues relevant to NV-101 need be addressed. The Sponsor stated that it will conduct a visual inspection of all cartridges in addition to the electronic check that occurs. The Division instructed the Sponsor to include this information in the NDA. The Sponsor inquired as to whether it should include manufacturing specifications in the NDA, since FDA inspects the manufacturing sites. The Division requested that the Sponsor summarize the information in the critical controls section of the NDA.

The Sponsor requested clarification regarding which part of the manufacturing process could be responsible for cartridges cracking during customer use of the product. The Division explained that the Sponsor should implement manufacturing controls to alleviate any product issues, such as cracking and/or defective cartridges, that were discovered during clinical trials and the rest of the development process. The Division stated that there may not be guidelines detailing the types of items for which specifications should be set, but that the *ICH Q6* guidance may be useful.

6. **Pre-filled cartridges and their immediate cartons are expected to provide adequate protection for the drug product and should be tested for the following:**

   a. **Accelerated testing.**

   b. **Temperature cycling, including extremes of low and high temperatures.**

   c. **Vibration.**

   d. **Package drop test to ensure integrity of all cartridge components.**

   e. **Loose cargo.**

   Discussion

   The Sponsor stated that it was not accustomed to the Agency requesting shipping validation information in NDAs. The Division responded that it is taking a more integrated approach to the inspectional and Chemistry, Manufacturing and Controls areas, and that this information should be included in the Sponsor's NDA.

   The Sponsor requested clarification regarding whether it should submit a summary or the full protocol for the drop testing, or whether raw test data are required. The Division stated that a summary of the testing would suffice and that the Agency's investigators will focus their inspections on any areas of concern raised by the summary information. The Division clarified that the Sponsor could perform the testing with validation lots of the product, since the firm does not have production lots at this time. The Division also advised the Sponsor to submit Novocol's test data for their standard product along with a justification for its applicability to NV-101.

   In response to the Sponsor's request for clarification regarding the suggestion to perform loose cargo testing, the Division informed the Sponsor that there is an American Society for Testing of Materials (ASTM) protocol for loose cargo testing. The Sponsor agreed to consult with ASTM in reference to this.

7. **Adequate data on the extractables and leachables should be provided in support of the elastomers used in the pre-filled cartridges. You may refer to relevant sections of USP <87>, <88>, and <661>.**

   Discussion

   This comment was not discussed at the meeting.

SUMMARY

The Sponsor summarized its understanding of the meeting as follows (includes Action Items):

1. The Division expects comments regarding the recently-submitted package samples from DMETS in approximately one month. The Division will consider DMETS' comments before providing the Sponsor with a response, as the Division is ultimately responsible for making decisions in this regard. The Sponsor understands that DMETS will likely have several packaging recommendations for the Sponsor.

2. The Sponsor will submit physical samples of the product as desk copies directly to the project manager as soon as possible after submitting the electronic NDA in eCTD format. The Sponsor will submit an array of samples similar to what the Sponsor submitted in November. One unit of each sample is acceptable to the Division.

3. It is expected that the Sponsor will be able to package NV-101 in standard dental cartridges. The Sponsor will continue to investigate ways to distinguish this product from dental anesthetics.

4. The Sponsor understands that the phentolamine mesylate degradation product [redacted] yielded a positive result in the *in vitro* Mammalian Chromosome Aberration Test (Study No. [redacted], and that the Division gained concurrence that this result is positive from Dr. David Jacobson-Kram. The Division recommends a third test be conducted, preferably an *in-vivo* micronucleus test. A negative result in this third test would likely alleviate the Division's concern regarding this product. b(4)

5. The Sponsor understands that the list of items it proposes to submit in support of process validation appears adequate.

6. The Sponsor will submit a Pharmaceutical Development Report that contains a summary, rather than raw data, with the NDA.

7. The Sponsor will include a summary of quality procedures for manufacturing in the NDA. Detailed Standard Operating Procedures (SOPs) will be reviewed by FDA investigators during facility inspections.

8. The Sponsor will submit a detailed summary of the drop testing, loose-cargo testing and other such tests. Alternatively, the Sponsor may submit Novocol's test data for their standard product along with a justification of why the testing is relevant to the NV-101 package.

9. It is acceptable to the Division for the Sponsor to remove study *NOVA 04-PK* from the proposed pool of four studies where dental procedures were not performed. This results in three pools—one including the five studies involving dental procedures, one including the three studies of healthy subjects, and one including study *NOVA 04-PK*.

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

/s/

Geraldine Smith
1/4/2007 01:28:09 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,095

Novalar Pharmaceuticals, Inc.
28202 Cabot Road
Suite 200
Laguna Niguel, CA 92677

Attention: Julius Knowles
President

Dear Mr. Knowles:

Please refer to the meeting between representatives of your firm and FDA on October 30, 2003. The purpose of the end-of-phase 2 meeting was to discuss the development plans for NV-101 (phentolamine mesylate for injection).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara Stradley
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Meeting Date: October 30, 2003

Location: Parklawn Building, Potomac Conference Room

IND: IND 65,095 (phentolamine mesylate injection)

Sponsor: Novalar Pharmaceuticals Inc.

Type of Meeting: End-of-Phase 2 meeting

Meeting Chair: Nancy Chang, M.D.
Division of Anesthetics, Critical Care and Addiction Drug Products, HFD-170

Minutes Recorder: Sara Stradley, M.S., Regulatory Project Manager

Novalar Pharmaceuticals	Title
Eckward Weber, MD	CEO
Jay Knowles	President
[redacted]	[redacted]
Mark Laviola, DDS	Clinical Trial Investigator
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

b(4)

FDA	Title
Bob A. Rappaport, MD	Division Director
Eric Duffy, PhD	Director, Division of New Drug Chemistry II
Nancy Chang, MD	Team Leader, Anesthetics
Arthur Simone, PhD, MD	Medical Reviewer
Dan Mellon, PhD	Supervisor, Pharmacology/Toxicology
David Lee, PhD	Biopharmacology Reviewer
Dionne Price, PhD	Statistics Reviewer
Fred Hyman, DDS	Dental Officer, DDDDP
Sara Stradley, MS	Regulatory Project Manager

Meeting Objective(s): The purpose of the End-of-Phase 2 meeting was to discuss the development plans for NV-101 (phentolamine mesylate for injection).

General Discussion: Following introductions, the discussion focused on the Sponsor's questions that were included in the September 29, 2003 meeting package. The Sponsor's questions and the Division's response are presented below in italicized text. Discussion is presented in normal text.

CMC

Question 1: Drug Substance-- Novalar will rely on the ——— 'Drug Master File (DMF) ——— for all drug substance information (a letter of authorization for DMF No. —— was submitted to FDA as Serial No. ——— Incoming active pharmaceutical ingredient (API) will be tested for conformance with the requirements of the current United States Pharmacopeia (USP) monograph for phentolamine mesylate. Once vendor validation is successfully established, testing may be reduced to confirmation of identity. Endotoxins and bioburdens testing will be performed on all batches, however, as these tests are not performed by the manufacturer. Is this acceptable to the Division? b(4)

FDA RESPONSE

DMF —— will be evaluated for its adequacy to support the NDA.

In addition to the USP testing, Novalar should test phentolamine mesylate for the process impurities and degradation products. The testing [acceptance criteria] should conform to the ICH Q3AR guidelines.

The drug substance is a mesylate salt ——— . In view of their potential [for] genotoxicity, they should be monitored in the drug substance and should be limited to e.g. NMT — PPM in the drug substance. Higher limits for these impurities will require information to support that these are not genotoxic in nature. b(4)

All batches of the drug substance should be tested for conformance to Novalar's acceptance specifications for the drug substance.

Endotoxin and bioburden testing on each batch may be carried out by a contract testing laboratory operating under cGMPs. However, the facility address, its registration number, etc. should be provided in the NDA.

Discussion
The Sponsor agreed.

Question 2: Drug Product--A formulation development study was performed in order to access the

b(4)

b(4)

FDA RESPONSE
It is acceptable to perform ——— of the product.

Provide detailed data with justification for the method of sterilization. Note that the media fills, filter integrity testing, and other sterilization validation requirements should conform to the Agency guidance "Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products."

Discussion
The Sponsor agreed.

Question 3: Drug Product--It is Novalar's understanding that dental cartridge products are commonly labeled with their nominal fill volume of 1.8 mL rather than the result of not less than (NLT) 1.7 mL as a result of testing per the requirements of USP<1>. Novalar has adjusted the formulation of NV-101 to deliver a dose of 0.4 mg in 1.7 mL and that commercial labeling will be based on the results of the USP<1> testing of the dental cartridges, considering the additional approximately — to be an acceptable parenteral overfill. Does the Division agree with this proposal? b(4)

FDA RESPONSE
Yes. Provide detailed justification in the NDA.

Discussion
The Sponsor agreed.

Question 4: Drug Product--The proposed drug product specification for NV 101 is listed in Table 2. The acceptance criteria will be re-evaluated in light of available stability data prior to NDA registration. Does the Division find the specification adequate for NDA-registration lots?

FDA RESPONSE
The specifications should include the following:

- *One specific ID test or two non-specific ID tests*
- *Specification for the degradation products conforming to ICHQ3BR (assuming a maximum daily dose of ≤ 10-mg):*
  - *Individual drug-related unspecified degradation product: NMT —* b(4)
  - *Total drug-related degradation products (sum of all reportable degradation products > —)*
  - *Provide data to support the safety of individual degradation products > —*

Discussion
The Sponsor asked for clarification on the acceptability of the diode array test. The Division stated this was an acceptable test.

Question 5: Drug Product--The proposed stability protocol for the NV-101 NDA registration lots is listed in Table 3. Long-term testing will be carried out at both controlled room temperature and under

refrigerated conditions, as there is insufficient stability data in this formulation to indicate whether NV-101 will have an acceptable room temperature stability profile or not. Are there additional tests or test points that the Division feels would be appropriate in addition to those listed?

FDA RESPONSE

- *Degradation products should be monitored.*
- *Delivered dose should be monitored*
- *Particulate matter and container closure integrity should be included in the intermediate and accelerated storage conditions*

Discussion

The Division stated that the room temperature data would be acceptable for accelerated stability data if the product is stored under refrigerated conditions.

Question 6: Drug Product--The NDA registration stability lots were manufactured at a formulation [redacted] b(4)

Does the Division agree that the scale of the NDA-registration lots is adequate to support manufacture at the proposed commercial scale?

FDA RESPONSE

General Expectations (ICHQ1AR)

- *Primary stability data from at least three primary batches of the drug product.*
- *The primary batches of the same formulation and packaged in the same container closure system as proposed for marketing.*
- *The commercial manufacturing process being identical to the one used in the manufacture of the primary stability batches.*
- *Assurance that the product of the same quality and meeting the same specification as that intended for marketing.*
- *Two of the three batches should be at least pilot scale batches, and the third one can be smaller if justified.*
- *Where possible, batches of the drug product should be manufactured by using different batches of the drug substance.*
- *Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied. Bracketing and matrixing proposals should be submitted for comment.*

Pilot versus Commercial Scale Batch

- *Pilot scale batch: A batch of a drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch, and generally, at a minimum, one-tenth that of a full production scale.*

- *NDA stability batches were manufactured at a formulation volume of* [redacted] *units per lot.* b(4)

- *Commercial production will involve formulation up to* [redacted] *units per batch.*

- *Based on the pilot scale batch size, a —— batch is expected to produce —— units per lot. Reconcile this discrepancy.* b(4)

- *Adequacy of the proposed scale of the NDA-registration lots is contingent upon the above criteria.*

Discussion
The Division reminded the Sponsor that their product should meet the specifications intended for marketing.

The Sponsor confirmed that batches of the drug product were manufactured by ——— b(4)

The Sponsor confirmed that there ——— container —

The Sponsor clarified that their calculations for the commercial batch scale were correct. The Sponsor stated that they did not want to formulate more than ——— . Their procedure involves b(4)

Question 7: Drug Product-- At this time, Novalar anticipates only 9 months of long-term stability data will be available at the time of NDA filing. Novalar proposes to update that NDA with data through 18 months during the ninth month of the NDA review. Presuming that the stability results are acceptable, an expiry of — nonths will be proposed on the basis of this data set. Does the Division agree with this proposal? b(4)

FDA RESPONSE

- *No.*

- *A 12-month long-term stability data along with the statistical analysis of all stability-indicating attributes is expected at the time of NDA filing. Note that if limited stability data are available for review, only a limited expiry will be possible.*

- *Stability updates to the NDA are acceptable.*
  - *Their evaluation towards expiration dating will depend on the timeliness of the submission and the available review time.*

- *ICH Q1E would be followed in the evaluation of the stability data.*

  - *The data evaluation for the estimation of shelf life would depend on the long-term storage conditions that would be identified in the stability studies.*

  - *While the expiration dating periods will normally be based only on the real time data, extent of extrapolation, if any, would depend on the quality of the long-term, intermediate and the accelerated storage stability data, and the information on the degradation pathways for the drug product.*

Discussion
The Division reiterated that 12 months of stability data should be included in the NDA at the time of filing. Updates are acceptable but their evaluation toward expiry dating will be based on

the timeliness of the submission.

PRECLINICAL

Question 8: Phentolamine Mesylate for Injection, USP has been marketed in the U.S. for 51 years, and one of its approved uses (blockade of alpha-adrenergically induced vasoconstriction) is essentially the same as the proposed clinical use of NV-101. However, NV-101 uses about one-twelfth as much drug. No new nonclinical issues are posed by the NV-101 drug product formulation or the dosage regimen for the reversal of dental anesthesia. Therefore, Novalar does not plan to conduct new nonclinical safety studies for NV-101 to support a future NDA. Does the Division concur?

FDA RESPONSE

- *No*
- *A local tolerance study should be completed for the NDA or prior to any planned multi-dose clinical trials. Histological analysis of the tissues must include sections containing neurological tissue to assess effects on these tissues.*
- *A standard battery of genetic toxicology studies will be required for an NDA. Further studies may be necessary should any positive results be obtained.*
- *Any impurity or degradation product that exceeds ICH specifications should be adequately qualified for the NDA.*
- *Impurities containing structural alerts for mutagenicity should be adequately qualified or reduced to NMT — %.*
- *Any novel excipients should be adequately qualified for the IND.*
- *In the interest of public health, the sponsor is encouraged to conduct fertility and post-natal development studies in a single species.*

Discussion

The Sponsor asked if a different tissue, other than the oral cavity, could be used for the local tolerance study. The Division stated that testing for local tolerance of tissue in the mouth would be ideal and suggested a dog model. The Sponsor should provide justification for the use of a different tissue and explain why that tissue is representative of the neuronal innervation and vascularization found in the oral cavity. The Division stated that systemic exposure to phentolamine should also be examined due to the different injection sites.

The Sponsor indicated that they were aware of [redacted] in their drug that exceeds ICH specifications and inquired what the appropriate qualification would entail. The Division indicated that a minimal genetic toxicology screen (one *in vitro* mutagenicity assay and one *in vitro* chromosome aberrations assay) plus a 14-day repeat dose toxicology study in a single species would be required. Regarding the qualification of an impurity with a structural alert for mutagenicity, the Division stated that the Sponsor should work with the manufacturer to determine the [redacted] their drug substance and determine if the process produces impurities with structural alerts for mutagenicity. b(4)

The Division reminded the Sponsor that any impurities containing structural alerts for mutagenicity should be adequately qualified or reduced to NMT [redacted]. To qualify such an impurity, the Division stated that a minimum of two genetic toxicity studies should be performed using the purified compounds. If the results are positive in either assay, a 2-year bioassay or a transgenic model should be completed, or the levels of a genotoxic impurity should be lowered to NMT 0.001%. b(4)

Question 9: The labeling for Phentolamine Mesylate for Injection, USP has nonclinical information that appears relevant to the future labeling of NV-101. Novalar anticipates that certain elements of that package insert might be part of the future labeling for NV-101 for the reversal of dental anesthesia. Does the Division have any guidance on what parts of the label for Phentolamine for Injection should be part of the label for NV-101?

FDA RESPONSE

- *Reproductive toxicology studies described in the phentolamine mesylate injection label should be included and updated (if available).*
  - *The actual study reports/published articles should be submitted with the NDA.*
  - *The exposure information should be updated to reflect drug product exposure for this indication.*

Discussion

The Division stated that the genetic toxicology data would also be included in the package insert.

HUMAN PHARMACOKINETICS

Question 10: Novalar proposed to [redacted] *in Section 10.2..2 of this document and the protocol synopsis is enclosed in Attachment 2. Does the Division concur that* [redacted] b(4)

FDA RESPONSE

Yes (see next slide for details)

Additional Comments (Human PK)

- *Since information in the Package Insert of currently approved drug product is sparse, provide additional information (e.g., from the data reported in the literature, etc.) in the future Labeling for NV-101.*

  Available information on the aspects of absorption, distribution, metabolism, elimination and special populations should be submitted in the future NDA. For example,

  - *Metabolism - route and extent of metabolism, metabolite activity, etc.;*
  - *Special populations – hepatic, renal impairment, etc., based on extent and elimination information;*

- *Drug interaction - phentolamine effect (PK and PD) on drugs likely to be co-administered, with particular emphasis on local anesthetic(s) containing vasocontrictor(s), and vice versa;*

- *Dose linearity – note that there is a proposal of using doses up to 0.8 mg (given as 2 inj.) in the protocol*

- *Pediatric information - currently the Sponsor is requesting "* ——————— *" in the future Labeling* b(4)

• *Proposed PK protocol : parameters should include CL and Vd.*

Discussion
The Division is not necessarily asking the Sponsor to conduct the basic standard battery of tests. The Division stated that additional information is needed for the label and that data in the literature may satisfy this requirement.

The Division recommended that the Sponsor put together a package describing their analytical method and the Sponsor agreed.

The Division stated that population PK study could be performed as part of the Sponsor's clinical trial. The Division stated they would be willing to review any protocol as time permits.

CLINICAL

Question 11: Novalar proposes that the primary efficacy endpoint for the phase 3 program is time to return of normal sensation in the lip after the use of a local anesthetic. Novalar proposes that the secondary efficacy endpoints for the phase 3 program are the time to return of normal sensation in the tongue and chin. The lip is more likely to become anesthetized and returns to normal sensation more slowly than other soft tissues such as chin, tongue, cheeks, and nose. Therefore, measuring normal sensation in the lip appears to be the most relevant way to assess reversal of soft-tissue anesthesia. Novalar has demonstrated in the phase 1 and phase 2 studies of phentolamine mesylate that measuring tactile sensation of the lip by palpation is a valid way to access reversal of soft-tissue anesthesia in dentistry. Does the Division concur that these endpoints are adequate for the demonstration of reversal of local anesthesia in dental procedure?

FDA RESPONSE

- *Resolution of the effects of the local anesthetics at the lip is a reasonable efficacy endpoint.*
- *Sites selected for assessment of local anesthetic reversal should be those for which reversal provides some benefit.*
- *Clarification is needed for the following:*
  - *Patients who fail to have lip numbness are to be excluded from the study, but may undergo their procedure. Is this to suggest that there is no benefit to be derived from phentolamine in this setting?*
    - *If so, consider lip numbness as one of the inclusion criteria for patients presenting for maxillary anesthesia.*
    - *If not, consider alternative assessment for effect of local anesthetic, e.g., numbness in the cheek or gingiva.*
- *Secondary endpoints, e.g., total resolution, will also be evaluated by FDA.*

Discussion
The Division stated that the Sponsor should provide evidence of the clinical benefits for reversing local anesthetic effects following dental, e.g., improved patient satisfaction, reduction in injury such as tongue or lip biting. The benefits should be in some way quantifiable, i.e., baseline patient satisfaction levels or injury rates need to be elucidated. The Division stated the clinical benefits of this drug product were not clearly evident and would be necessary to perform a benefit-risk analysis as studies proceed. The Sponsor inquired about use of patient surveys as a means of assessing patient satisfaction. The Division stated this could be useful; however, it would be strongly recommended that the survey(s) be validated. The Sponsor agreed to evaluate various surveys.

Question 12: In the phase 2 study (Study No. NOVA 03-001), NV-101 demonstrated a statistically significant reduction in the time to normal sensation in anesthetized tissues in patients who received local anesthesia with either lidocaine with epinephrine, articaine with epinephrine, prilocaine with epinephrine, or mepivocaine with levonordefrin (i.e., these are the four FDA approved local anesthetic drug products containing a vasoconstrictor used in dentistry). In the proposed phase — tudy (Study No. b(4)

Novalar intends to state in the labeling for NV-101 that NV-101 reverses anesthesia induces by the use of a local anesthetic containing a vasoconstrictor (I.e., all of the four approved anesthetic drug products containing a vasoconstrictor). Does the Division concur that the design of these studies could support a claim for the reversal of all vasoconstrictor-containing local anesthetics if it can be demonstrated that NV-101 produces such reversal with each anesthetic?

FDA RESPONSE
Labeling will be more fully addressed following submission of the NDA. The label contents may be based on findings from the safety/efficacy trials and/or those reported in the literature.

To the extent that the data show significant, reproducible reversal of local anesthetic effects, versus a comparator, a claim may be supported. The following would need to be addressed for FDA to consider a general indication for reversal of local anesthetics containing a vasoconstrictor:

- *The mechanism for reversal has not been fully elucidated such that demonstration of efficacy with a few members of a drug class can be extrapolated to the entire class. A general claim would require demonstration that phentolamine exerts its effect by reversing vasoconstriction caused by vasoconstrictors co-administered with local anesthetics.*

- *The full range of concentrations of available vasoconstrictors, as well as the full range of local anesthetics (e.g., bupivicaine) need to be evaluated.*

The claim may need to be limited to those local anesthetics/ vasoconstrictors studied.

Discussion
The Division stated that there should be a clear understanding of the mechanism of action to allow a broad based claim.

Question 13: The results of the phase 2 clinical study of NV-101 (Study No. NOVA 03-001) demonstrated a statistically significant reduction in the time to normal sensation in anesthetized tissues in patients who received local anesthesia with a vasoconstrictor-containing anesthetics. The reductions in the time to normal sensation in the lip, chin, and tongue were approximately 40-50%, or 50-70 minutes. Does the Division concur that this level of efficacy constitutes a clinical benefit?

FDA RESPONSE

- *The study report for NOVA 03-001 has received only a preliminary review at this point.*

- *The reductions in time to normal sensation appear to be clinically significant. However, in addition to evaluating the reductions in time, the Division will consider the meaningfulness of the benefits, e.g., possible injury, patient satisfaction with anesthetic.*

- *Exceptions were noted, e.g.,*
  - *Mandible/articaine/epinephrine – only 2% reduction for return of sensation to the lip*
  - *Maxilla/prilocaine/epinephrine – had a -9% in "tingling" time.*

  The relative significance of these findings should be evaluated, i.e., were they related to the investigator, performance of the block or reversal injection, etc.

Discussion

The Sponsor noted a mistake in the slide presentation.

- *Mandible/articaine/epinephrine – only ~~2%~~ 21 % reduction for return of sensation to the lip*
- *Maxilla/prilocaine/epinephrine – had a -9% in "tingling" time.*

Question 14: If the Division concurs with the primary efficacy endpoint of return of normal sensation in the lip (Question 11), Novalar proposes that the phase 2 study (NOVA 03-001) can be considered one of the two adequate and well controlled studies to support a future NDA filing of NV-101 for the proposed indication. Does the Division concur?

FDA RESPONSE (Clinical)

- *A trial may constitute a pivotal trial provided:*
  - *There is adequate support for the dose used.*
  - *Efficacy endpoints and safety monitoring were appropriate.*
  - *Inclusion/exclusion criteria allow a population to be studied that are representative of the population which ultimately will be treated with the drug.*

- *If NOVA03-001 is used as a pivotal trial, whether or not it will support an approval action is a matter for review. Specific concerns identified regarding the use of 03-001 as a pivotal trial include the following.*

  - *Dose ranging studies evaluated only 0.02, 0.08 and 0.4 mg.*
  - *Limited types of blocks and procedures were studied.*
  - *Labeling would reflect that only healthy subjects 10 years of age and older have been included.*
  - *Repeat dosing (to 0.8 mg) was not evaluated*

Discussion
The Division reminded the Sponsor that the label will include the types of blocks used in the clinical studies and suggested that the Sponsor evaluate a full range of blocks. The Sponsor should consider all of the ways (e.g. blocks, techniques, procedures, sites)their product might be actually used in the clinical setting.

The Division requested clarification on why the dose ranging studies went from 0.08 to 0.4 mg with no intermediate dose. While the dosing studies are likely to be adequate for an NDA, justification that the proposed dose is neither too high nor too low would be useful. The Sponsor will provide information.

Soft tissue anesthesia for the tongue is important. It has been noted that if a block is missed, the lip may not be numb but the tongue may be numb. The Sponsor should consider if it is appropriate to exclude such patients, as it appears likely that such patients might be treated by practitioners in the clinical setting. Therefore, exclusion of such patients should be justified.

Question 15: The summary of a proposed phase – linical trail (Study No.) is found in Section 10.2.1 of this document and the full protocol is enclosed in Attachment 1. Does the Division concur with the study design and that this study, in addition to the Phase 2 study (Study No. NOVA 03-001), will b(4)

FDA RESPONSE

- *The proposed trial appears to be adequate.*
- *Ultimately, the efficacy database must demonstrate safety and efficacy in the target population for which the drug is intended. This would generally include, among other things, the following.*
  - *Reasonable representation of blocks/infiltrations to be reversed and procedures for which the blocks will be used, e.g., cleanings, scalings, restorations, extractions, fixed prosthodontics.*
  - *Patients in good and poor health.*
  - *A full range of ages for the patients including geriatric populations.*
  - *A significant number of patients exposed to the proposed highest-labeled dose.*

Discussion
The Division reiterated that the product should be tested in the same manner as it will reasonably be expected to be used in clinical practice.

Question 16: Children ages 10-17 were included in the phase 2 study (Study No. NOVA 03-001)(N=24), and b(4)

" Does the Division concur with this approach, and does the Division have a minimum number of subjects in this age group that should be included in the phase – study?

FDA RESPONSE
The label will reflect the populations studied. Off-label use is a consideration in the overall benefit/risk analysis for the drug.

We strongly encourage you to evaluate, at some point, the use of phentolamine in children of all ages who may benefit from reversal of local anesthetic.

Approximately 100 children with an adequate age distribution should provide a sufficient safety database. Adequacy of the database size will depend in large part upon clinical findings, dosing, and demographic considerations.

Discussion
The Division questioned the age cutoff of 10 years of age. It would seem that the younger population is at higher risk for lip biting. The Division reminded the Sponsor about pediatric exclusivity. The Sponsor stated that they felt it would be very difficult to test their product in a young population. The Sponsor is concerned about the reliability of the reporting data. The Sponsor stated it would be hard to collect efficacy data in the younger population versus just safety data. The Division stated it might be acceptable to look primarily at safety data in children, but that if the sponsor wished to do so, they would need to provide adequate justification or evidence that it would be appropriate to extrapolate efficacy from older children and adults. The Division advised the Sponsor to talk with pediatric dentists about the use of this drug in the pediatric population. The Sponsor agreed.

The Sponsor questioned if a pediatric study could be a post marketing commitment. However the Division stated that this should be addressed at the time of the NDA filing.

Question 17: Phentolamine Mesylate for Injection, Usp was approved by FDA 51 years ago and is approved for reversion the local effects of an alpha-agonist infiltration or extravasation. The dosage regimen for this indication is a rapidly delivered series of injections that deposit 5 to 10 mg of phentolamine into the effected tissues. The dosage regimen for NV-101 reversal of dental anesthesia is a single 0.4 mg injection or up to 0.8 mg (given as 2 injections) of phentolamine into the anesthetized tissues (i.e., less than one-twelfth of the approved maximum dose of 10 mg). Based on the extensive previous human experience with phentolamine for injection, Novalar proposes that the number of patients necessary for the clinical safety database for NV-101 NDA be equal to that in the clinical efficacy database (i.e., approximately 250 patients for the Phase 2 and 3 trials will have received NV-101). Does the Division concur?

FDA RESPONSE
The size of the safety database is dependant on the findings of the trials and what is currently known about the drug.

Systemic absorption of phentolamine does not appear to be a significant issue. However, the drug has not been studied previously for mucosal and possible neurotoxic effects. Additionally, there are some safety concerns regarding mesylate compounds.

The safety of phentolamine administered after 4-5 carpules of local anesthetic have been given should be evaluated.

Thorough evaluation of about 300 patients given the doses proposed for marketing could provide a sufficient database assuming no safety issues are identified, and a broad range of patients (in terms of demographics, health status, injection sites, procedures and dose) are assessed.

Discussion
The Division stated that the studies seemed reasonable but a minimum of 300 patients would be needed to provide an adequate database. A significant number of these patients should be exposed to the highest proposed dose of phentolamine (0.8mg).

Question 18: The labeling for the currently approved drug product Phentolamine Mesylate for Injection, USP has clinical information that appears to be relevant to future labeling for NV-101. A copy of the package insert for Phentolamine Mesylate for Injection, USP is included in Attachment 3. Novalar anticipates that certain elements of this current package might be part of the future labeling for NV-101 for the reversal of dental anesthesia. Does the Division have any guidance on what parts of the label for Phentolamine for Injection should be part of the label for NV-101?

FDA RESPONSE
Information from the Description, Contraindications, Warnings, Precautions, and Adverse Reactions sections of the current label will likely carry over to the Novalar label. It may be necessary to provide additional information to these sections based on results of the current studies.

- *Additional label information that should be provided in an NDA includes the following.*
  - *Dose ranging study information.*
  - *Effects of the drug on bleeding following the procedures.*
  - *Information concerning local tissue or nerve toxicity.*
  - *Use of the drug when local irritation/abscess is present.*
  - *Usefulness of the drug when other blocks, e.g. palatal infiltration or superior alveolar nerve block, are utilized.*

Consideration should be given to distinguishing the phentolamine carpules from those of local anesthetics. This could be the first non-anesthetic, dental drug product that would be available in a standard carpule

Discussion
The Division stated that the Sponsor should ensure that their drug product can be readily differentiated from dental local anesthetics, both individually and as a class (i.e. the product should not appear to be an extension of the current line of local anesthetics.). The Sponsor stated that it is the same size as other carpules but plan to change the color to distinguish it from other carpules.

The Division also questioned the reproducibility and feasibility of the technique requiring injection of phentolamine in the same tract as the local anesthetic, and how often a dentist in a typical busy practice could actually return to the exact location of the original injection site. The Sponsor stated that this was not examined directly but that the greatest effect is in the area where the local anesthetic was given. It is unclear how far away the phentolamine mesylate injection could be from the original site of injection and still work properly. The Division encouraged the Sponsor to explore these issues.

The potential risk of increased bleeding following local anesthetic reversal should also be evaluated.

STATISTICS

Question 19: The statistical analysis plan for the proposed _____ *included in Section 10 of the protocol found in Attachment 1. Does FDA agree that this plan will adequately test the results in a manner that will support the proposed indication?* b(4)

FDA RESPONSE
Yes, the analysis plan is acceptable.

Discussion
The Division asked the Sponsor to clarify how censored data would be incorporated into the proposed analysis. The Sponsor replied that censored observations were not anticipated due to the nature of the study design. The Sponsor further commented that the analysis plan would be modified to account for censored observations, if needed.

OTHER QUESTIONS

Question 20: Novalar plans to prepare the future NDA using the Common Technical Document (CTD) format. Is that acceptable to the Division?

FDA RESPONSE
Yes.

Discussion
There was no discussion.

Question 21: Does the Division have a preference for NDA filing format (electronic format or paper format)

FDA RESPONSE
Electronic

Refer to Guidance for Industry; Providing Regulatory Submissions in Electronic Format--NDAs
(www.fda.gov/cder/guidance/2353fnl.pdf)
(www.fda.gov/cder/guidance/2867fnl.pdf)

Discussion
There was no discussion.

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

/s/

Sara Stradley
11/24/03 02:27:31 PM