CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-159

CHEMISTRY REVIEW(S)

NDA 22-159

Ora Verse®
(phentolamine mesylate)
Injection

Novalar Pharmaceutical, Inc.

Elsbeth Chikhale, Ph.D.
ONDQA – DPA I – Branch II
for
Division of Anesthesia, Analgesia and Rheumatology Products

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Chemistry Review Data Sheet

1. NDA 22-159

2. REVIEW #: 1

3. REVIEW DATE: 14-DEC-2007

4. REVIEWER: Elsbeth Chikhale, Ph.D.

5. PREVIOUS DOCUMENTS: N/A
   Meeting minutes EOP2 meeting on 10/30/2003
   Meeting minutes teleconference on 1/14/2005
   Meeting minutes Pre-NDA meeting on 12/8/2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	09-APR-2007
Amendment to original[1]	19-OCT-2007
Amendment to original[2]	26-NOV-2007 (advanced e-mail)

   1) The 10/19/07 amendment provides for a response to an information request from the Agency dated 10/3/07.
   2) The 11/26/07 amendment provides for an advanced e-mail response to an information request from the Agency dated 11/9/07. The target date for the official submission is 12/19/07.

7. NAME & ADDRESS OF APPLICANT:

Name: Novalar Pharmaceutical Inc.

Address: 12555 High Bluff Drive, Suite 300
San Diego, CA 92130

Representative: Laura A. Navalta (Vice President of Clinical Operations)

Telephone: (858) 436 - 1130

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ora Verse®

b) Non-Proprietary Name (USAN): phentolamine mesylate

c) Code Name/#: NV-101 (drug product)
CAS 65-28-1 (phentolamine mesylate)

d) Chem. Type/Submission Priority:

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(2) application.

10. PHARMACOL. CATEGORY: α-1 and α-2 adrenergic receptor antagonist

11. DOSAGE FORM: injection, solution

12. STRENGTH/POTENCY: 0.235 mg/mL (0.4 mg/dose of 1.7 mL)

13. ROUTE OF ADMINISTRATION: intraoral submucosal injection

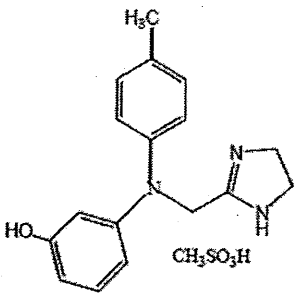
14. Rx/OTC DISPENSED: _x_Rx ___OTC

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

_____SPOTS product ___ Form Completed
__x__Not a SPOTS product

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

Phentolamine mesylate:



Chemistry Review Data Sheet

Chemical name: Phenol,3-[[(4,5-dihydro-1*H*-imidazol-2-yl)methyl](4-methylphenyl)amino]-, methanesulfonate (salt)
Molecular Formula: $C_{17}H_{19}N_3O \cdot CH_4O_3S$
Molecular Weight: 377.46

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]				1	Adequate	September 6, 2007	Reviewed by Elsbeth Chikhale, Ph.D.
				3	Adequate	December 22, 2005	Reviewed by J. Boal, Ph.D.
				3	Adequate	December 22, 2005	Reviewed by J. Boal, Ph.D.
				1	Adequate	October 29, 2007	Reviewed by Elsbeth Chikhale, Ph.D.
				3	Adequate	August 6, 2004	Reviewed by S. Read

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,095	Phentolamine Mesylate, Injection
NDA	8-278	Regitine (phentolamine mesylate) RLD

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Biometrics	N/A		
EES	Acceptable	10/19/07	
Pharm/Tox	N/A		
CDRH	N/A		
Clinical Pharmacology	N/A		
Methods Validation	Acceptable	12/14/07	Elsbeth Chikhale, Ph.D.
DMETS	Ora Verse® is acceptable	8/3/07	
DDMAC	Ora Verse® is acceptable	5/4/07	
EA	Categorical exclusion granted (consult not needed)	12/14/07	Elsbeth Chikhale, Ph.D.
Microbiology	Approvable, pending response to deficiencies/ comments.	11/13/07	Stephen Langille, Ph.D.

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 22-159

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation from the standpoint of chemistry, manufacture and controls is APPROVAL pending:

- Final labeling (which will be done in coordination with the clinical division)
- An APPROVAL recommendation from Microbiology (current recommendation is APPROVABLE from Microbiology).

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

1) Drug Product

The drug product is a sterile solution for injection, containing 0.235 mg/mL phentolamine mesylate, USP (i.e. 0.4 mg/dose of 1.7 mL) for intraoral submucosal administration. This NDA is submitted as a 505(b)2. The reference listed drug (RLD) is Regitine (phentolamine mesylate) injection (5 mg/vial) (NDA 8-278), which is approved but not currently marketed in the U.S. The proposed drug product, Ora Verse®, is indicated for the reversal of soft tissue anesthesia and associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor. The container closure system for the drug product is a blister package containing 10 glass dental cartridges each with a rubber plunger and cap. The formulation of the proposed commercial product and of the registration stability batches are the same. The proposed storage condition is at room temperature (25 °C, excursion permitted to 15-30 °C), and the proposed expiry date is 36 months for the drug product. The provided stability data support the proposed shelf life of 36 months when stored at room temperature conditions.

A list of Microbiology deficiencies and comments has been sent to the applicant and a response is currently pending. Therefore, the NDA remained approvable from the Microbiology point of view.

2) **Drug Substance**

Phentolamine Mesylate, USP:
The drug substance, phentolamine mesylate, USP, is a synthetic small molecule. It is a white to off-white, odorless, crystalline powder. It is sparingly soluble in water, soluble in alcohol, and slightly soluble in chloroform. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of phentolamine mesylate are provided in the Drug Master File (DMF) ——— A Letter of Authorization to allow the Agency to review this DMF was provided in the NDA. This DMF was reviewed and found adequate on 9/10/98 (Chem. Review #3 by U.S. Atwal, Ph.D.) in support of ———. Several updates have been submitted since that review, which are reviewed in support of this NDA (review #4 dated 9/6/07 by Elsbeth Chikhale, Ph.D.). The proposed specifications and analytical methods for phentolamine mesylate comply with the requirements described in the current United States Pharmacopeia (USP) monograph for phentolamine mesylate. Several additional tests are included in the drug substance specifications and are performed by the drug product manufacturer. For any future changes (post-marketing) to the manufacturing process of the drug substance, the applicant has committed to determine the presence of ——— ——— impurities using the GC-MS method described on pg. 12 of this review.

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

The product is administered using the same location and same technique (infiltration or block injection) used for the administration of the local anesthetic (containing a vasoconstrictor). The recommended dose is ½ cartridge of Ora Verse when ½ cartridge of local anesthetic has been used, 1 cartridge of Ora Verse when 1 cartridge of local anesthetic has been used, and 2 cartridges of Ora Verse when 2 cartridges of local anesthetic have been used.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation from the standpoint of chemistry, manufacture and controls is APPROVAL pending final labeling and Microbiology recommendation.

III. Administrative

A. Reviewer's Signature: in DFS

B. Endorsement Block: in DFS

C. cc Block: in DFS

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X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Elsbeth Chikhale
12/14/2007 02:11:27 PM
CHEMIST

Ali Al-Hakim
12/14/2007 03:06:07 PM
CHEMIST

Memorandum to File

To: NDA 22-159; OraVerse® (phentolamine mesylate) Injection
From: Elsbeth Chikhale, Ph.D. – Chemistry Reviewer
Subject: Microbiology consult review.
Date: February 11, 2008

Applicant: Novalar Pharmaceuticals Inc.
Proposed Proprietary Name: OraVerse®
Established Name: phentolamine mesylate
Dosage form and strength: 0.235 mg/mL (0.4 mg/vial of 1.7 mL)
Route of Administration: intraoral submucosal injection
Indications: For the reversal of soft tissueanesthesia and associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor.

Note:
The consult Product Quality Microbiology Review #2 dated 30 January, 2008 by Stephen Langille, Ph.D. has recommended approval from the standpoint of product quality microbiology. CMC concurs with this recommendation. There are no remaining CMC issues and NDA 22-159 is recommended for APPROVAL from CMC perspective.

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/s/

Elsbeth Chikhale
2/11/2008 04:37:46 PM
CHEMIST

Ali Al-Hakim
2/12/2008 09:29:34 AM
CHEMIST

NDA 22-159

Ora Verse®
(phentolamine mesylate)
Injection

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Name: Novalar Pharmaceutical Inc.
Address: 12555 High Bluff Drive,
Suite 300 San Diego, CA 92130

Indication: Reverse the soft tissue anesthesia associated with dental injections of local anesthetic agents.

Presentation: The container closure system for the drug product is a blister package containing 10 glass dental cartridges each with a rubber plunger and cap. The drug product is a sterile solution for injection, containing 0.235 mg/mL Phentolamine mesylate, USP (i.e. 0.4 mg/dose of 1.7 mL) for intraoral submucosal administration.

EER Status: Acceptable 13-Mar-2007

Consults:

Microbiology:	Acceptable
Methods Validation:	Agency revalidation not recommended
DMETS/DDMAC:	Acceptable
EA:	Categorical exclusion granted under 21 CFR §25.31(b)

Original Submission: 09-APR-2007

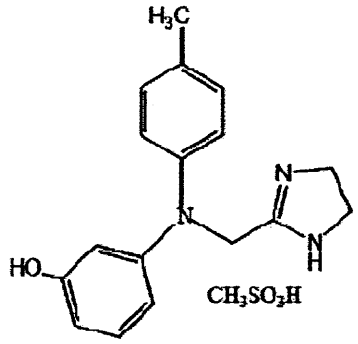
Amendments: 19-OCT-2007
20-DEC-2007

Drug Substances

The drug substance, Phentolamine Mesylate, USP, is a synthetic small molecule. It is a white to off-white, odorless, crystalline powder. It is sparingly soluble in water, soluble in alcohol, and slightly soluble in chloroform. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of phentolamine mesylate are provided in the Drug Master File (DMF) — held by ——————. A Letter of Authorization to allow the Agency to review this DMF was provided in the NDA. This DMF was reviewed and found adequate in support of ——————. Several updates have been submitted since that review, which are reviewed in support of this NDA (review #4 dated 9/6/07 by Elsbeth Chikhale, Ph.D.). b(4)

The proposed specifications and analytical methods for phentolamine mesylate comply with the requirements described in the current United States Pharmacopeia (USP) monograph for phentolamine mesylate. Several additional tests are included in the drug substance specifications and are performed by the drug product manufacturer.
Molecular structure of the drug substance is provided below.

Phentolamine mesylate:



Conclusion: Information for the drug substance is acceptable.

Drug Product:
The drug product is a sterile solution for injection, containing 0.235 mg/mL phentolamine mesylate, USP (i.e. 0.4 mg/dose of 1.7 mL) for intraoral submucosal administration. The proposed drug product, Ora Verse®, is indicated for the reversal of soft tissue anesthesia and associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor. Inactive excipinets include Edetate disodium, D-mannitiol, sodium acetate, acetic acid, sodium hydroxide, _____ b(4)
Tests and acceptance criteria include appearance, identification, assay, purity, pH, delivered dose, Particulates, sterility, bacterial endotoxins, and syringeability.
The container closure system for the drug product is a blister package containing 10 glass dental cartridges each with a rubber plunger and cap. The proposed storage condition is at room temperature (25 °C, excursion permitted to 15-30 °C), and the proposed expiry date is 36 months for the drug product. The provided stability data support the proposed shelf life of 36 months when stored at room temperature conditions.

Conclusion: Drug product information is acceptable.

Overall Conclusion:
From a CMC perspective, the application is recommended for **approval.**

Ali Al-Hakim, Ph.D.
Branch Chief
Branch II/DPA I/ONDQA

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/s/

Ali Al-Hakim
2/8/2008 06:28:45 PM
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Initial Quality Assessment
Branch V
Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)

OND Division:	Anesthesia, Analgesia and Rheumatology Products
NDA:	22-159
Applicant:	Novalar Pharmaceutical, Inc.
Stamp date:	April 09, 2007
PDUFA Date:	February 09, 2008
Trademark:	NV-101
Established Name:	Phentolamine mesylate Injection
Dosage Form:	Solution
Route of Administration:	Injection
Indication:	Reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor
Pharmaceutical Assess. Lead:	Ali Al-Hakim, Ph.D.
ONDQA Fileability:	YES √ NO___
Comments for 74-Day Letter:	YES ___ NO √

Summary, Critical Issues and Comments

A. Summary

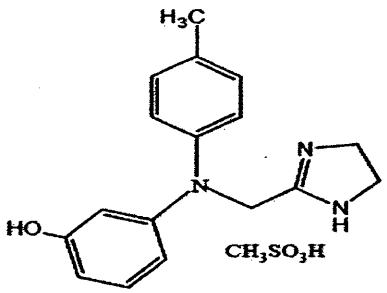
The is a 505(b)(2) new drug application based on the listed drug, Regitine®. The sponsor reported that drug product, Phentolamine mesylate, is a sympatholytic competitive α-adrenergic blocker that non-selectively antagonizes both α1 and α2 receptors. NV-101 (phentolamine mesylate) Injection is being developed 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.

The drug product is an injection, solution. The primary container closure system is a ——— standard 1.8 mL dental cartridge that is labeled to deliver 1.7 mL. The strength is 0.4mg. b(4)

B. Review, Comments and Recommendations

Drug Substance Synthesis/Manufacturing Process

The Chemical structure and chemical name of the drug substance are shown below



Chemical Name

Phenol,3-[[(4,5-dihydro-1H-imidazol-2-yl)methyl](4- methylphenyl)amino]-, methanesulfonate (salt).

The CMC information for the drug substance is provided in DMF —. Therefore, the applicant provided a letter of authorization for the manufacturer of the drug substance; —— regarding the CMC information for the drug substance, phentolamine mesylate, USP. b(4)

Manufacturing/Synthesis Flow Chart of the drug substance

b(4)

described in the above flow chart. The final step is —— affording the final drug substance. The complete CMC information is provided in the DMF. b(4)

4 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Review issues for the drug product specifications:

- The Proposed limits for impurities/degradation product including:

b(4)

- Justification for proposed limit for each impurity and for total impurities
- Proposed particulate matter limits for injection and if the proposed limits are based on actual batch test data or on the maximum allowable limits as described in USP
- Microbial tests. The reviewer may consult with the microbiology reviewer regarding evaluating and assessing of these tests and the subsequent validation procedure for the sterilization process.

The followings are additional important issues and attributes which are related to the drug product that need to be assessed by the reviewer:

- Pharmaceutical development report and significant changes between the clinical and the NDA batches. The sponsor provided a well documented pharmaceutical development report highlighting the critical parameters and process controls developed and utilized throughout the drug product development leading to the final formulation and, therefore, the manufacturing process of the drug product.
- Any significant differences between pre clinical batches and NDA registration batches
- Batch analysis and consistency of test data obtained from various batches
- Stability test data and the proposed expiry dating of 36 months

Container/Closure System

The issues need to be assessed with respect to the integrity of the container/closure system

Labeling issues b(4)

CMC labeling issues for the package insert, primary and secondary container (e.g., names, description, how supplied, indication for use, storage statement) should be evaluated regarding the patient instructions (see attached samples). The reviewer may need to consult with DEMTS regarding these issues.

Method validation package is included in the NDA and needs to be evaluated depending on the nature of the test methods and if there are novel/complex methods need to be validated further by FDA laboratory.

C. **Critical issues for review and recommendation**

During reviewing and evaluation of the quality of the CMC information provided in this NDA, the primary reviewer may consider performing the assessment with emphasis on the following topics and any other related issues that may have a potential impact on the quality of the drug substance and the drug product.

Drug Substance issues

CMC information in the DMF including any updates/changes which may include the following critical issues:

- Review of the DMF with respect to the CMC of the drug substances information and any updates, amendments, and annual reports that contain significant CMC information.
- Assessment and subsequent evaluation of the structural alert studies report (——— impurities) and related test methods/data regarding the adequacy of the above methods in addressing FDA concerns at EOP2 meeting. b(4)
- Stability updates and the proposed retesting period for the drug substance

Drug Product Issues

- Compatibility of the phentolamine mesylate substance with the excipients for such parenteral dosage form
- Compatibility of the drug product with the container/closure system (particulates, discoloration, participation, etc)
- Integrity of — during the filling process b(4)
- Cap pressure, fill volume, and visual appearance of the ——— filled cartridges
- Justification/scientific rationale for the overfill
- Microbiological testing during the filling procedure
- Justification and test controls for the bulk drug product holding time
- In-process controls testing including bioburden test, sterilization, filter integrity, etc.
- Pharmaceutical development report and significant changes between the clinical and the NDA batches. The sponsor provided a well documented pharmaceutical development report highlighting the critical parameters and process parameters developed and utilized throughout the drug product development leading to the final formulation and manufacturing process of the drug product.
- Any significant differences between pre clinical batches and NDA registration batches
- Batch analysis/Consistency of test data between various batches
- Stability test data with respect to the proposed expiry dating.

With respect to drug product specification

- The proposed limits for impurities/degradation product based on batch data which should include:
  - ⌐
  - b(4)
  - ⌋
- Justification for proposed limit for individual impurity and total impurities
- Proposed particulate matter limits for injection and if the proposed limit is based on actual batch data or just on the maximum allowable limits as described in USP

- Microbial tests. The reviewer may consult with the microbiology reviewer regarding evaluating and assessing of these tests and the subsequent validation procedure for the sterilization process.

Regarding the reference standard

- Primary reference standards and the supportive information with respect to characterization and structural elucidation and purity

Stability

Evaluation of the stability data with respect to the proposed 36 months expiry dating

With respect to container closure system

-
-
-
- Validation of the bulk drug product manufacturing process and the packaging process.

b(4)

Labeling issues:

CMC labeling issues for the package insert and secondary container (e.g., description, how supplied, indication for use, storage statement) should be evaluated regarding the patient instructions (see attached samples).

D. **Comments for 74-day Letter**: None

E. **Recommendation for fileability**: The NDA is recommended to be filed because there is a considerable amount of CMC information and data which are suitable for evaluation and assessment based on the FDA and related ICH guidelines for submitting the appropriate CMC information for New Drug Application.

- **Recommendation for Team Review:** It is recommended that NDA be viewed by one reviewer because drug substance is included in a DMF and the drug product is a fill-line process.
- **Consults**

  The reviewer, in conjunction with project manager, should initiate the following consults/requests as early as possible (see fileability template below).

Ali Al-Hakim, Ph.D. Pharmaceutical Assessment Lead	05/18/2007 Date
Ravi Harapanhalli, Ph.D. Branch Chief	05/18/2007 Date

Fileability Template

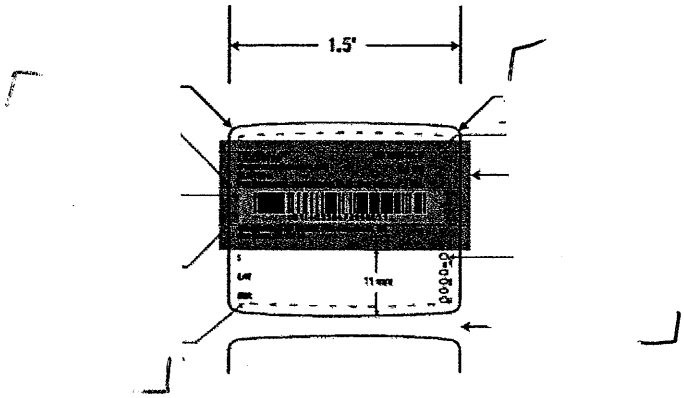
	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?			To be determined by the reviewer
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			Yes. LOA to IND 65,095
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		Validation Report
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated?		√ √	Statistics DMETS/ODS Microbiology

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LOA Included	Status
			Yes	
			Yes	
			Yes	
			Yes	
			Yes	
			Yes	

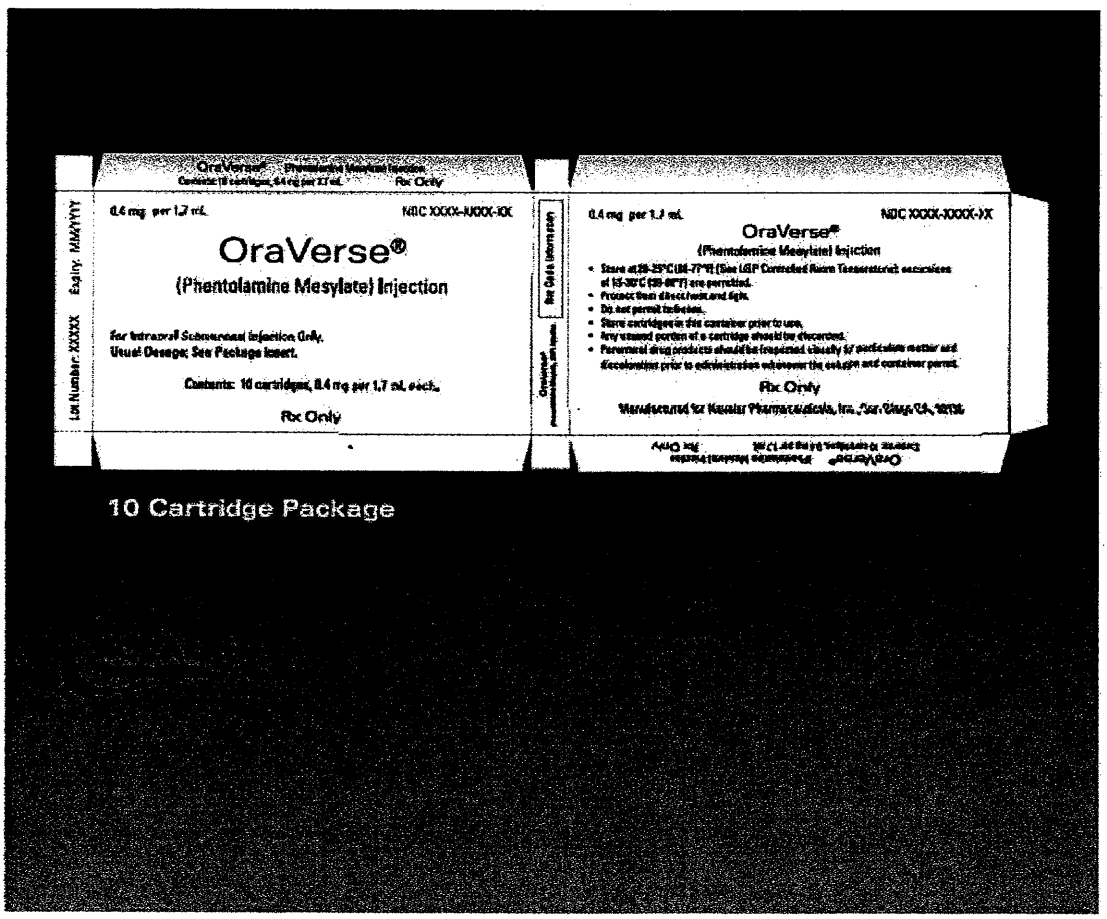
b(4)

Cartridge label



b(4)

Carton label



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/s/

Ali Al-Hakim
5/18/2007 11:15:24 AM
CHEMIST

Ravi Harapanhalli
5/25/2007 04:14:13 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22159/000
Org Code : 170
Priority : 3S
Stamp Date : 09-APR-2007
PDUFA Date : 09-MAY-2008
Action Goal :
District Goal: 11-DEC-2007

Sponsor: NOVALAR
NO CITY, , XX

Brand Name : PHENTOLAMINE MESYLATE INJECTION
Estab. Name:
Generic Name: PHENTOLAMINE MESYLATE
Dosage Form: (INJECTION)
Strength : 0.235 MG/ML

FDA Contacts:			
	G. SMITH	Project Manager (HFD-560)	301-796-2204
	E. CHIKHALE	Review Chemist	301-796-1659
	A. AL HAKIM	Team Leader	301-796-1323

Overall Recommendation: ACCEPTABLE on 19-OCT-2007by S. ADAMS (HFD-325) 301-796-3193

Establishment : CFN : [redacted] FEI : [redacted] b(4)
NOVOCOL PHARMACEUTICAL CANADA
25 WOLSELEY CT.
CAMBRIDGE, , CA

DMF No: AADA:

Responsibilities: [redacted] MANUFACTURER

Profile : [redacted] OAI Status: POTENTIAL OAI b(4)
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-AUG-07
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

DMF No: [redacted] AADA:

b(4)

Responsibilities: [redacted]

Profile : [redacted] OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-OCT-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION