CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-159

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA No.	22-159
Applicant Name	Novalar Pharmaceuticals, Inc.
Date of Submission	April 9, 2007
PDUFA Goal Date	May 9, 2008
Proprietary Name / Established (USAN) Name	OraVerse/ phentolamine mesylate
Dosage Forms / Strength	Injection solution / 0.4 mg
Proposed Indication(s)	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.
Action:	*Approval*

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Arthur Simone, M.D., Ph.D.
Statistical Review	Feng Zhou, M.S. / Dionne Price, Ph.D.
Pharmacology Toxicology Review	Elizabeth Bolan, Ph.D. / Dan Mellon, Ph.D.
CMC Review/OBP Review	Elsbeth Chikhale, Ph.D. / Ali Al-Hakim, Ph.D.
Microbiology Review	Stephen Langille, Ph.D. / James McVey, Ph.D.
Clinical Pharmacology Review	David Lee, Ph.D. / Suresh Doddapaneni, Ph.D.
DDMAC	Michelle Safarik, PA-C
DSI	Sherbet Samuels, R.N., M.P.H. / Constance Lewin, M.D.
CDTL Review	N/A
OSE/DMETS	Kristina C. Arnwine, PharmD, Safety Evaluator / Cathy Miller, M.P.H. / Linda Kim-Jung, PharmD, Team Leader
OSE/DDRE	N/A
OSE/DSRCS	N/A
Other	Fred Hyman, D.D.S. M.P.H, Dental Officer, DDDP Ann Marie Trentacosti, M.D., SEALD Team

CDTL = Cross-Discipline Team Leader
DDMAC = Division of Drug Marketing, Advertising and Communication
DDRE = Division of Drug Risk Evaluation
DMETS = Division of Medication Errors and Technical Support
DSI = Division of Scientific Investigations
DSRCS = Division of Surveillance, Research, and Communication Support
OND = Office of New Drugs
OSE = Office of Surveillance and Epidemiology
SEALD = Study Endpoints and Labeling

1. Introduction

OraVerse contains phentolamine mesylate, an alpha-adrenergic blocking agent, as the active ingredient in a new dosage form. The applicant seeks to market the product as a cartridge, which is to be used to reverse the effects of local anesthetics on soft tissues (i.e., lip and tongue) following dental procedures.

Phentolamine was originally approved in 1952 (NDA 8-278). It was marketed as Regitine® for the diagnosis and treatment of pheochromocytoma, and for the treatment and prevention of dermal necrosis following intravenous administration or extravasation of norepinephrine. The applicant is relying on the Agency's previous findings of safety and efficacy for Regitine®. The original NDA holder, Ciba (now Novartis) discontinued marketing in 2000; a generic version was approved in 1998 (ANDA 40-235) and is currently available in the United States.

The application was submitted on April 9, 2007, and the original due date for the application was February 9, 2008; however, due to the submission of additional data on January 23, 2008, the review time clock was extended by three months to May 9, 2008.

This memorandum will comment on the regulatory requirements that needed to be addressed in order to obtain the indication sought by the applicant; the design of the studies submitted in support of the indication, including the efficacy endpoints and the analyses performed by the review team; the safety findings reported from the clinical studies; and the package insert proposed by the applicant.

2. Background

The applicant's clinical development program consisted of nine clinical trials, including an adult and a pediatric pharmacokinetic study, dose-ranging studies, a pediatric efficacy trial, and three efficacy and safety trials in adults and older pediatric patients. Two of the efficacy trials in adults were conducted under a Special Protocol Assessment agreement. The applicant's interactions with the Agency during the course of their development program were substantial, including an End-of-Phase 2 meeting, a pre-NDA meeting, and two meetings and a teleconference to discuss the Special Protocol Assessment advice letters that were issued regarding their Phase 3 protocols.

Among the issues the applicant needed to address in the course of their development program was the need to demonstrate that reversal of the anesthetic effects following a dental procedure resulted in a clinical benefit. The applicant developed two metrics: a questionnaire to assess the patient's perception of their recovery from anesthesia, referred to as the Soft Tissue Anesthesia Recovery (STAR) questionnaire, and the Functional Assessment Battery, referred to as the FAB tests. The second of the two metrics consisted of an assessment of the patient's ability to speak, smile, drink liquids, and not drool. The FAB assessment was performed by the patient, and by a treatment-blinded observer.

3. CMC/Device

The product is to be packaged in glass dental cartridges, each with a rubber plunger and cap. The container closure system for the cartridges is a blister package containing 10 cartridges. During the course of the review, several deficiencies were noted in the application which prevented the microbiology reviewer from making an assessment as to whether the product could be reliably manufactured in a sterile fashion. The additional information submitted by the applicant was able to address all of the concerns, and the final recommendation by the Chemistry, Manufacturing, and Control and Microbiology reviewers was for an approval of the application.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The applicant conducted a single-dose local tolerance study and a battery of genetic toxicology studies with phentolamine mesylate and [redacted] impurities/degradants found in the drug product, [redacted] A Segment I male fertility study with oral administration of phentolamine mesylate was also conducted. Repeat-dose toxicology, reproductive and developmental toxicology, and carcinogenicity studies were not required for this 505 (b)(2) application for the proposed patient population. b(4)

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Drug-drug interactions studies were not performed in the traditional since, since the systemic levels of phentolamine following intraoral injection of the doses proposed by the applicant were very low. However, the effects of intraoral injection of phentolamine on the pharmacokinetics of a previously administered anesthetic and vasoconstrictor were evaluated and found to not be affected in a clinically significant manner.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

The microbiology data submitted in the application were pertinent to the manufacture of the drug product; there were no clinical microbiology data submitted or required in this application.

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

Primary and Secondary Endpoints

The primary endpoint of the clinical trials was the return of normal sensation to the lip following anesthesia induced by a combination of a local anesthetic and vasoconstrictor. Secondary endpoints which involved sensation included the return to normal sensation to the tongue, cheek, chin, nose and teeth.

Patients were instructed in the technique to assess the return to normal sensation (palpation of the soft tissues, i.e., tongue, lip, cheek, and nose, and by the grinding of the teeth to assess the teeth's sensation), and the assessment technique was codified in the protocol. Patients were included in the efficacy assessment only if they were able to successfully demonstrate the technique.

Other secondary endpoints included the STAR questionnaire and FAB test scores, two metrics that were developed by the applicant, discussed with the Agency, and incorporated into the two studies that were the subject of Special Protocol Assessment agreements. These endpoints were designed to assess the clinical relevance of the reversal of the soft tissue anesthesia.

The STAR questionnaire consisted of 12 questions assessing the patient's subjective perception of their concerns for self-inflicted injury while their soft tissues were anesthetized, and of their ability to function at baseline levels for speaking, drinking, smiling, and not drooling. An abbreviated version of the metric, STAR-7, utilized seven of the twelve questions, and was used in the pivotal trials. Both questionnaires were validated for use in adults.

The FAB tests scores were not formally validated, but the use of a composite score based on normal or abnormal findings for each function provided a means for assessing the patient's changes from, and return to, baseline. Its use as a secondary endpoint provided substantiation for the STAR questionnaire findings of complete recovery from the soft tissue anesthesia.

Efficacy Findings

There was a substantial and significant difference between the treatment group and control with respect to the time to recovery of normal sensation of the lip for all four studies. The following table summarizes the results of the primary endpoint, time to recovery of normal sensation; it is adapted from Dr. Simone's review.

Table 1: Median Time to Recovery of Normal Sensation

	(*Number of Subjects*) Median time to recovery of normal sensation (in minutes)[1] (95% Confidence Interval)					
	Lip			**Tongue**		
Study Number	**OraVerse**	**Sham**	**p-value**	**OraVerse**	**Sham**	**p-value**
NOVA 04-100	(*122*) 70 (65, 80)	(*121*) 155 (140, 165)	<0.0001	(*93*) 60 (55, 70)	(*103*) 125 (110, 135)	<0.001
NOVA 04-200	(*120*) 50 (45, 60)	(*119*) 133 (115, 145)	<0.0001	NA	NA	NA

Study Number	(*Number of Subjects*) Median time to recovery of normal sensation (in minutes)[1] (95% Confidence Interval)					
	Lip			Tongue		
	OraVerse	Sham	p-value	OraVerse	Sham	p-value
NOVA 03-001	(*61*) 70 (55, 101)	(*61*) 155 (135, 165)	<0.0001	(*30*) 74 (60, 92)	(*31*) 105 (90, 125)	<0.0011
NOVA 05-PEDS (Overall)	(*72*) 60 (45, 75)	(*43*) 135 (105, 65)	<0.0001	NA	NA	NA
NOVA 05-PEDS (Mandible)	(*38*) 60 (45, 75)	(*19*) 180 (135, 180)	<0.0001	(*32*) 45 (30, 45)	(*16*) 112.5 (45, 150)	<0.0001
NOVA 05-PEDS (Maxilla)	(*34*) 60 (45, 75)	(*24*) 113 (75, 150)	<0.0002	NA	NA	NA

[1]Kaplan-Meier medians and stratified Log-Rank Test p-values

Evaluation of the secondary endpoints also identified a substantial and significant difference in the return to a normal STAR-7 and FAB scores in the two studies that utilized these metrics. These results are summarized in the two tables below, adapted from Dr. Simone's review.

Table 2: Time to Normal STAR-7 (modified Intent-to-Treat Population)

Study	OraVerse		Sham		Time Difference (% Reduction)	Stratified Log-Rank p-value
	N	Median (95% CI*)	N	Median (95% CI*)		
NOVA 04-100	118	90 (60, 90)	121	150 (120, 150)	60 (40%)	<0.0001
NOVA 04-200	109	60 (60, 90)	111	120 (120, 150)	60 (50%)	<0.0001

* Confidence interval

Table 3: Time to Normal FAB Score (modified Intent-to-Treat Population)

Study	OraVerse		Sham		Time Difference (% Reduction)	Stratified Log-Rank p-value
	N	Median (95% CI*)	N	Median (95% CI*)		
NOVA 04-100	103	60 (50, 75)	103	120 (110, 130)	60 (50%)	<0.0001
NOVA 04-200	100	60 (50, 65)	89	105 (85, 125)	45 (43%)	<0.0001

* Confidence interval

It was noted during the review that a substantial number of patients were reported as having protocol deviations, approximately 50% of which consisted of deviations from the proper use of the FAB tool. Most of the deviations consisted of failure to conduct the assessments at the protocol-specified time point. In order to assess the impact of these deviations, an analysis was performed on the data excluding all the patients who had been reported to have had a protocol deviation in the FAB assessment; there was no significant impact on the overall conclusions. The results of this analysis are summarized in the table below, adapted from Dr. Simone's review.

Table 4: Time to Normal FAB Score (Patients with no FAB-related Protocol Deviations)

Study	OraVerse		Sham		Time Difference (% Reduction)	Stratified Log-Rank p-value
	N	Median (95% CI*)	N	Median (95% CI*)		
NOVA 04-100	64	55 (45, 75)	71	120 (110, 130)	65 (54%)	<0.0001
NOVA 04-200	67	55 (45, 60)	64	98 (80, 125)	43 (44%)	<0.0001

* Confidence interval

I concur with Dr. Simone's assessment that the application contains the sufficient data to reach the following conclusions regarding Oraverse relative to placebo:

1. OraVerse substantially reduces the time to return to normal sensation in the lip and tongue following dental nerve blocks with local anesthetics containing a vasoconstrictor in adult patients and pediatric patients over the age of 12 years.
2. OraVerse reduces the time required to return to baseline levels in both the perception of the ability to function normally and the concern for a risk of self-inflicted injury to the tongue, lip, or cheek
3. OraVerse substantially reduces the time to return to normal sensation in the lip in patients 6 to 11 years of age.

Although the application does contain some safety data in patients younger than 6 years of age, there are insufficient data to make any conclusions regarding the efficacy of OraVerse in this age group.

4. Safety

The safety database consisted of nine clinical studies, five of which involved patients undergoing dental procedures, and four of which involved healthy subjects. The total number of patients exposed to a dose of OraVerse was 418. The number of patients, stratified by age and dose is summarized in the table below, adapted from Dr. Simone's review:

Table 5: Number of Patients Exposed to OraVerse, by Age Group

	Dose of OraVerse				Control
Age	0.2 mg N = 83 n (%)	0.4 mg N = 284 n (%)	0.8 mg N = 51 n (%)	Total N = 418 n (%)	Total N = 359 n (%)
3 – 11 years	82 (99)	27 (10)	0	109 (26)	56 (16)
12 – 17 years	0	36 (12)	9 (18)	45 (11)	40 (11)
18 – 64 years	1 (1)	194 (68)	40 (78)	235 (56)	237 (66)
≥ 65 years	0	27 (10)	2 (4)	29 (7)	26 (7)

The safety assessments included evaluation for the hemodynamic effects commonly associated with the use of phentolamine, including blood pressure and heart rate changes, as well as the occurrence of cardiac arrhythmias. Local tissue irritation was evaluated with frequent oral examinations and the incidence of pain, either due to the injection itself or the early dissipation of the anesthesia, was evaluated with the use pain-scale score.

There were no deaths, serious adverse events (SAEs), or patient drop-outs due to adverse events reported in the clinical trials.

The most commonly reported adverse event, identified as occurring in ≥ 1% of the patients, and differing from the control group by > 1.5% were: bradycardia, hypertension, abdominal pain, and administration site conditions (injection site reaction or pain, jaw or oral pain, and tenderness). The incidence of these adverse events is summarized in the table below, adapted from Dr. Simone's review.

Table 6: Common Adverse Events (≥ 1%, and Differing by >1.5% from Control)

Adverse Event	OraVerse N = 481 n (%)	Control N = 388 n (%)	Sham Control Alone N = 359 n (%)
Cardiac disorders			
Bradycardia	7 (1)	1 (< 1)	0
Hypertension	9 (2)	5 (1)	0
Gastrointestinal disorders			
Abdominal pain	4 (1)	1 (<1)	0
General disorders and administration site conditions			
Injection site reaction	4 (1)	1 (<1)	0
Injection site pain	24 (5)	14 (4)	14 (4)
Jaw pain	4 (1)	0	0
Oral pain	4 (1)	1 (<1)	1 (<1)
Tenderness	4 (1)	1 (<1)	0

Further review of the data regarding the most commonly reported adverse events resulted in the conclusion that the observed bradycardia was not likely to be related to the phentolamine, as alpha-adrenergic blockade is more likely to result in tachycardia and that the other adverse events, although potentially causally related to the study treatment, were not clinically significant.

One of the studies incorporated Holter monitoring to assess for rhythm abnormalities. Although abnormalities were noted, they occurred in both treatment groups, and were not clinically significant.

There was only one event in the safety database that was identified as a possible lingual nerve injury, in a 14-year old patient who underwent a filling in a tooth in the right lower quadrant. The case report form indicated that the patient had two injections of prilocaine with epinephrine over the right mandible 20 minutes apart, and two study drug injections approximately 45 minutes after the second local anesthetic injection. At 6, 7, and 8 hours after the study drug injections, the patient reported mandibular jaw soreness; her oral exam was reported as normal up to 3 hours after study drug administration, after which no further oral exams were performed. The patient reported that approximately 30 minutes after discharge (corresponding to approximately 3 hours and 45 minutes after study drug injection), she experienced a tingling sensation in the right anterior portion of her tongue, which diminished over the course of the following three days. During the follow-up visit, three days after the injection, it was noted that her tongue deviated approximately 1 cm to the right when extended, with normal movement of the tongue and no fasciculations noted. The remainder of the exam was reported as normal. She was lost to follow-up to the study after that visit;

however, the case report form indicated that she was reportedly seen by her local dentist ten times after her participation in the study and she never reported any symptoms to him.

The changes in lingual sensation reported by the patient are consistent with lingual nerve injury, but it is difficult to ascribe it to the study drug alone. Potential etiologies include mechanical injury from the needle of any one, or a combination, of the four injections, compression injury from injection into the neuronal sheath, or chemical injury from any one, or a combination, of the agents that were used. These injuries are relatively rare and generally resolve with time, and any study that would be intended to resolve whether the increased manipulation and infiltration required for the administration of OraVerse would require a significant number of patients in order to be adequately powered to detect a difference. There is also the likelihood that the information obtained would not substantially alter the risk:benefit profile, unless the injuries are found to be more symptomatic or of longer duration. At this point in time, it is sufficient to ensure that the label indicates the potential for these types of adverse events.

5. Advisory Committee Meeting

The product is not a new molecular entity (NME), and no issues were identified during the course of the review which necessitated the need for the convening of an Advisory Committee meeting.

6. Pediatrics

The applicant is seeking approval for use in pediatric patients [redacted] years of age, and a waiver for newborns and infants (up to age 2), since the first teeth are just beginning to erupt between the ages of 4 and 13 months, and there is minimal need for dental procedures that would require a local anesthetic with a vasoconstrictor. b(4)

The application has safety data in pediatric patients down to the proposed age group, and review of the safety database did not reveal any substantial difference in the safety profile between the following age groups: 3 – 11 years of age, 12 – 17 years of age, and 18 – 64 years of age. However, adequate data on the efficacy of the drug product was only provided down to age 6; efficacy was not assessed in patients younger than 6 years, only safety and tolerability.

The application was taken to the Pediatric Review Committee (PeRC) on April 30th, and they concurred with the Division's assessment that the studies in the 6 to 18 year-old age group were adequate, that studies were needed in the 2 to 6 year-old age group, and that it was appropriate to waive study requirements in the 0 to 2 year-old age group. The committee also recommended that the label only reflect that efficacy and safety were evaluated in the 6 to 18 year-old group.

7. Other Relevant Regulatory Issues

Division of Medication Errors and Technical Support

In a consult finalized today, DMETS also had several recommendations regarding the dental cartridge and the package and container labels. Representatives from DMETS (Cathy Miller,

M.P.H., and Linda Kim-Jung, Pharm.D.) indicated that the recommendations regarding the package and container labels were not approvability issues.

The recommendation proposed by DMETS regarding the dental cartridge involved the lack of markings that would permit accurate administration of doses less than an entire cartridge. Although it is an accurate observation that the cartridge currently does not have any increments of measure, I do not feel that the lack of markings poses a safety issue and is, therefore, unnecessary for the current recommended method of dosing and administration stipulated in the package insert. At this time, a patient will either receive a full cartridge or ½ of a cartridge, depending on the amount of anesthetic agent delivered, which will also be administered in a similar fashion (i.e., a full cartridge or ½ of a cartridge). Since the same operator will most likely administer the anesthetic agent and the OraVerse, it is expected that the estimation as to what constitutes ½ of a cartridge will be consistent. Furthermore, administration of slightly more than ½ of a cartridge will not pose a safety concern. However, if the applicant ever intends to pursue an indication where more accurate dosing is required, for example in younger pediatric patients, then the need for incremental markings on the cartridge will need to be revisited.

The Division shared its perspective with DMETS, and they concurred with the Division that the lack of markings on the cartridge is not a safety concern for the proposed indication.

Division of Scientific Investigation Audits
The Division of Scientific Investigations conducted site inspections for two clinical sites and found the studies appeared to have been conducted adequately, and that the data generated from these sites appeared acceptable in support of the application.

Consults
A consult was obtained from the Division of Dermatologic and Dental Products (Fred Hyman, D.D.S. M.P.H), to assess whether there was a need for OraVerse in the pediatric patient population. The question posed in the consultation request was whether the published literature contained any information on the benefits of local anesthesia reversal in children who underwent dental procedures.

Dr. Hyman noted in his consultation response that although minimal information can be located in the published literature to substantiate the incidence of oral tissue injury in children resulting from residual local anesthesia after a dental procedure, the consensus among pediatric dentists is that this risk exists. He indicated that the magnitude of the problem is sufficient that the American Academy of Pediatric Dentistry issued a warning to dentists about the possibility of self-induced soft tissue trauma in children as a complication of local anesthetic use and advises risk minimization. Dr. Hyman concluded that the use of a product that reduces the duration of post operative local anesthesia would be of medical benefit to the pediatric population.

There are no other unresolved relevant regulatory issues.

8. Labeling

I concur with Dr. Simone that the major changes to the label proposed by the applicant revolved around the following issues:

1. References to the efficacy of NV-101 in pediatric subjects less than 6 years old should be removed.
2. NV-101 should only be recommended for use in patients older than 6 years of age and weighing more than [redacted]). b(4)
3. [redacted] b(5)

Several discussions were held with the applicant regarding the package insert and all remaining issues regarding the package insert were resolved during a teleconference held on May 7, 2008.

The Division of Medication Errors and Technical Support (DMETS) provided a review of the proposed trade name, OraVerse, and had no objection to its use.

There is no need for a Medication Guide based on the findings for the safety and efficacy profiles and the proposed indication.

9. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval.

- Risk Benefit Assessment

I concur with the review team's assessment that the risk:benefit ratio of OraVerse therapy remains favorable for patients 6 years of age and older, who have undergone dental procedures which required the use local anesthetics.

- Recommendation for Postmarketing Risk Management Activities

None.

- Recommendation for other Postmarketing Study Requirements

Although the applicant has provided safety date in patients less than 6 years of age, the application did not contain sufficient information to assess the efficacy in this age group. As noted by Dr. Hyman's consultation response, the use of a product that reduces the duration of post operative local anesthesia would be of medical benefit to the pediatric population in this age group.

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/s/

Rigoberto Roca
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MEDICAL OFFICER