Important Safety Information

In clinical trials, the most common adverse events with OraVerse (phentolamine mesylate) vs. control were post-procedural pain (6% vs. 6%), injection site pain (5% vs. 4%), tachycardia (5% vs. 6%), bradycardia (2% vs. 0.3%) and headache (3% vs. 4%). Following parenteral use of phentolamine in non-dental indications, myocardial infarction and cerebrovascular spasm and occlusion have been reported, usually in association with marked hypotensive episodes producing shock-like states. Although such effects are uncommon with OraVerse, clinicians should be alert to the signs and symptoms of tachycardia and cardiac arrhythmias, particularly in patients with a history of cardiovascular disease, as these symptoms may occur with the use of phentolamine or other alpha-adrenergic blocking agents.
Phentolamine mesylate (PM) safely and effectively reduces the duration of local anesthetic-induced soft-tissue numbness and its associated functional deficits. Nevalar’s OraVerse, an injectable formulation of PM, is the first and only local dental anesthesia reversal agent that accelerates the return to normal sensation and function after procedures involving intraoral submucosal injection of a vasoconstrictor-containing local anesthetic.

Reduced Numbness

PM has been shown to reduce post-anesthesia upper lip median recovery times from 133 minutes to 50 minutes in adults and adolescents. By decreasing the duration of residual soft-tissue anesthesia by approximately 50%, patients feel normal more quickly and the risk of soft-tissue injury may be reduced.2,3

When the 12 dentists who participated in this Dental Product Shopper evaluation were asked about reduced lip numbness, 1 rated it as excellent, 7 rated it as very good, and 4 rated it as good. Reduced tongue numbness was rated as excellent by 1 evaluator, as very good by 6, and as good by 5. Citing “quicker working time” as a feature he’d like to see improved, 1 dentist said “reversal takes about an hour.” One evaluator noted that “patients like being able to lose the numbness quickly…to go out to lunch after an appointment,” and another evaluator said his patients “didn’t mind the ‘additional’ injections and said their feeling returned faster than expected!”

Ease of Use

Ease of use of OraVerse was rated as excellent by 8 evaluators and as very good to good by 4. An evaluator who said he would definitely recommend and purchase OraVerse cited “some learning curve in knowing when to inject it for maximum benefit.” Another dentist said that “while well marked, perhaps the cartridges should have a brighter marking to avoid confusion with local anesthetic cartridges.” A West Deptford, NJ evaluator called OraVerse “simple for all to understand” and a dentist in prac-
tice in Trussville, AL commented that “ease of delivery is great and effectiveness is beyond question.”

Patient Reaction
In a manufacturer-conducted survey, 86% of 370 patients reported that OraVerse improved their dental experience and 82% said they would recommend it to family and friends. When the Dental Product Shopper evaluators were asked about patient reaction, 2 rated it as excellent, 6 rated it as very good, and 4 rated it as good. One evaluator said “patients were very happy,” and another said many of his patients “were surprised that a product like this existed and were enthusiastic about trying it.” The Red Bank, NJ pediatric dentist who asked his patients to text him when the numbness was gone said the messages “were very positive and made them think about the product and mention it to others.”

The manufacturer states that OraVerse is indicated only for adults and for children age 6 years and older and weighing at least 33 pounds. One evaluator, who said he would definitely recommend and purchase it, cited “indication for children under age 6… the ones most likely to bite themselves after a local” as a feature he’d like to see improved.

A Havre de Grace, MD evaluator who said it has “limited use in my practice” explained that “most patients want to be numb longer after lengthy treatment.” A Denver, CO dentist exclaimed, “My patients loved it!” This same dentist gave all features a rating of excellent. “I see many business executives who need to coordinate their visits with hectic schedules, and have very good feedback from patients saying they were pleased to be able to return to their work duties promptly.”

Overall Satisfaction
While 8 dentists cited cost as a concern, 11 said they would definitely or probably recommend OraVerse to colleagues, with comments such as “if the price were lower it would be a great adjunct to dental procedures.” Overall satisfaction was rated as excellent by 2 evaluators, as very good by 6, as good by 3, and as fair by 1. One evaluator said, “It’s nice to have another tool to increase patient satisfaction.”

References
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OraVerse™ safely and effectively. See full prescribing information for OraVerse.

OraVerse (phentolamine mesylate) Injection
Initial U.S. Approval: 1952

INDICATIONS AND USAGE
OraVerse is indicated for the reversal of soft tissue anesthesia, i.e., anesthesia of the lip and tongue, and the associated functional deficits resulting from an intranasal submucosal injection of a local anesthetic containing a vasoconstrictor. OraVerse is not recommended for use in children less than 6 years of age weighing less than 15 kg (33 lbs). (3)

DOSE FORM AND STRENGTH
0.4 mg/2.7 mL solution per cartridge (3)

CONTRAINDICATIONS
None (4)

WARNINGS AND PRECAUTIONS
Myocardial infarction, cerebrovascular spasm, and cerebrovascular occlusion have been reported to occur following the intranasal or intramuscular administration of phentolamine, usually in association with marked hypertensive episodes or shock-like states which occasionally follow parenteral administration.

Tachycardia and cardiac arrhythmias may occur with the use of phentolamine or other alpha- adrenergic blocking agents. (5.1)

ADVERSE REACTIONS
The most common adverse reaction with OraVerse (incidence >= 5%) is injection-site pain. (5)

To report SUSPECTED ADVERSE REACTIONS, contact Neovia at 1-800-688-1421 or FDA at 1-888-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS
- Use in pediatric patients less than 6 years of age or <= 15 kg (33 lbs) is not recommended. (8.4)
- In pediatric patients weighing less than 35 kg (65 lbs), the maximum dose of OraVerse recommended is 1/2 cartridge (0.2 mg). (8.4)

Revised: January 2009

FULL PRESCRIBING INFORMATION: CONTENTS*
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2.2 Dosing in Special Populations
3. DOSAGE FORMS AND STRENGTHS
4. CONTRAINDICATIONS
5. WARNINGS AND PRECAUTIONS
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1. INDICATIONS AND USAGE
OraVerse is indicated for reversal of the soft tissue anesthesia, i.e., anesthesia of the lip and tongue, and the associated functional deficits resulting from an intranasal submucosal injection of a local anesthetic containing a vasoconstrictor.

OraVerse is not recommended for use in children less than 6 years of age weighing less than 15 kg (33 lbs).

2. DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
The recommended dose of OraVerse is based on the number of cartridges of local anesthetic with vasoconstrictor administered:

<table>
<thead>
<tr>
<th>Amount of Local Anesthetic Administered</th>
<th>Dose of OraVerse</th>
<th>Dose of OraVerse (e.g.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/4 Cartridge</td>
<td>0.2</td>
<td>15</td>
</tr>
<tr>
<td>1 Cartridge</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>2 Cartridges</td>
<td>0.8</td>
<td>2</td>
</tr>
</tbody>
</table>

OraVerse should be administered following the dental procedure (using the same location(s) and technique(s) (filtration or block injection) employed for the administration of the local anesthetic.

Note: Do not administer OraVerse if the product is discolored or contains particulate matter.

2.2 Dosing in Special Populations
In pediatric patients weighing 15-30 kg, the maximum dose of OraVerse recommended is 1/2 cartridge (0.2 mg).

(Nota: in pediatric patients under 6 years of age weighing less than 15 kg (33 lbs) is not recommended.

A dose of more than 1 cartridge (0.4 mg) of OraVerse has not been studied in children less than 15 years of age.)

3. DOSAGE FORMS AND STRENGTHS
0.4 mg/2.7 mL solution per cartridge

4. CONTRAINDICATIONS
None.

5. WARNINGS AND PRECAUTIONS
5.1 Cardiovascular Events
Myocardial infarction, cerebrovascular spasm, and cerebrovascular occlusion have been reported to occur following the intranasal or intramuscular administration of phentolamine, usually in association with marked hypertensive episodes or shock-like states which occasionally follow parenteral administration.

Tachycardia and cardiac arrhythmias may occur with the use of phentolamine or other alpha-adrenergic blocking agents. Although such effects are uncommon after administration of OraVerse, clinicians should be alert to the signs and symptoms of these events, particularly in patients with a prior history of cardiovascular disease.

6. ADVERSE REACTIONS
In clinical trials, the most common adverse reaction with OraVerse that was greater than the control group was injection site pain.

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Dental patients were administered a dose of either 0.2, 0.4 or 0.8 mg of OraVerse. The majority of adverse reactions were mild and resolved within 48 hours. There were no serious adverse reactions and no discontinuations due to adverse reactions.

Table 1 lists adverse reactions where the frequency was greater than or equal to 5% in any OraVerse dose group and was equal to or exceeded that of the control group.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>OraVerse</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Patients with AEs</td>
<td>15 (13)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>5 (6)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Post procedural pain</td>
<td>3 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

An examination of population subgroups did not reveal a differential adverse reaction incidence based on the basis of age, gender, or race.

Results from the pain assessments in Study 1 and Study 2 involving mandibular and maxillary procedures, respectively, indicated that the majority of dental patients in both OraVerse and control groups experienced no or mild oral pain, with less than 10% of patients in each group reporting moderate oral pain with a similar distribution between the OraVerse and control groups. No patient experienced severe pain in these studies.

6.2 Adverse Reactions in Clinical Trials
Adverse reactions reported by less than 3% but at least 2 dental patients receiving OraVerse and occurring at a greater incidence than these receiving control, included diarrhea, facial swelling, increased blood pressure/hypertension, injection site reactions, jaw pain, ear pain, pancreatitis, pruritus, tenderness, upper abdominal pain and vomiting.

The majority of these adverse reactions were mild and resolved within 48 hours. The few reports of pancreatitis were mild and transient and resolved during the same time period.

6.3 Post Marketing Adverse Reactions Reports from Literature and Other Sources
The following adverse reactions have been identified during postapproval parental use of phentolamine mesylate.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Acute myoglobinuric renal failure has been reported in otherwise healthy male patients who received phentolamine in combination with other vasoconstrictors for prolonged periods of time. The combination of drugs may potentiate arterial vasoconstriction and result in acute renal failure.

7. DRUG INTERACTIONS
There are no known drug interactions with OraVerse.

7.1 Lidocaine and Epinephrine
When OraVerse was administered as an intranasal submucosal injection 30 minutes after injection of a local anesthetic, 2% lidocaine HCI with 1:100,000 epinephrine, the lidocaine concentration increased immediately after OraVerse intranasal injection. Lidocaine AUC and Cmax values were not affected by administration of OraVerse. OraVerse administration did not affect the PK of epinephrine.

8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. OraVerse should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

Oral administration of phentolamine to pregnant rats and mice at doses at least 24 times the recommended dose (based on a 60 kg human) resulted in slightly decreased growth and slight skeletal immaturity of the fetuses. Immaturity was manifested by increased incidence of incomplete or unossified calvarial and phalangeal nuclei of the hind limb and of incompletely ossified sternebrae. At oral phentolamine doses at least 50 times the recommended dose (based on a 60 kg human), a slightly lower rate of implantation was found in the rat. Phentolamine did not affect embryonic or fetal development in the rabbit at oral doses at least 20 times the recommended dose (based on a 50 kg human). No teratogenic or embryotoxic effects were observed in the rat, mouse, or rabbit studies.

8.3 Nursing Mothers
It is not known whether OraVerse is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when OraVerse is administered to a nursing woman. The unknown risks of limited infant exposure to phentolamine through breast milk following a single maternal dose should be weighed against the known benefits of breastfeeding.

9. FULL PRESCRIBING INFORMATION
9.1 Pregnancy
Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. OraVerse should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

Oral administration of phentolamine to pregnant rats and mice at doses at least 24 times the recommended dose (based on a 60 kg human) resulted in slightly decreased growth and slight skeletal immaturity of the fetuses. Immaturity was manifested by increased incidence of incomplete or unossified calvarial and phalangeal nuclei of the hind limb and of incompletely ossified sternebrae. At oral phentolamine doses at least 50 times the recommended dose (based on a 60 kg human), a slightly lower rate of implantation was found in the rat. Phentolamine did not affect embryonic or fetal development in the rabbit at oral doses at least 20 times the recommended dose (based on a 50 kg human). No teratogenic or embryotoxic effects were observed in the rat, mouse, or rabbit studies.

8.3 Nursing Mothers
It is not known whether OraVerse is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when OraVerse is administered to a nursing woman. The unknown risks of limited infant exposure to phentolamine through breast milk following a single maternal dose should be weighed against the known benefits of breastfeeding.
8.4 Pediatric Use
In clinical studies, pediatric patients between the ages of 3 and 17 years received Oravense. The safety and effectiveness of Oravense have been established in the age group 6-17 years. Effectiveness in pediatric patients below the age of 6 has not been established. Use of Oravense in pediatric patients between the ages of 6 and 17 years old is supported by evidence from adequate and well-controlled studies of Oravense in adults, with additional pediatric data. The effectiveness of Oravense in pediatric patients ages 12-17 years old (Study 1 (mandibular procedure) and 2 (maxillary procedure)) and ages 6-11 years old (Study 3 (maxillary and mandibular procedures)) has been established in pediatric patients. In the age group 6 years old, dosage in pediatric patients may need to be limited based on body weight. (See Dosage and Administration 2)

8.5 Geriatric Use
Of the total number of patients in clinical studies of Oravense, 55 were 65 and over, and 21 were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10. OVERDOSAGE
No deaths due to acute poisoning with phenelzine have been reported.

Overdosage with parenterally administered phenelzine is characterized chiefly by cardiovascular disturbances, such as tachycardia, hypotension, and possibly shock. In addition, the following might occur: restlessness, headache, sweating, palpitation, tachycardia, diaphoresis, nausea, vomiting, diarrhea, or hypotension.

There is no specific antidote. Treatment consists of appropriate monitoring and supportive care. Substantial decreases in blood pressure or other evidence of shock-like conditions should be treated vigorously and promptly.

11. DESCRIPTION
Phenelzine mesylate is phenyl-2-(1,2,4,5-tetrahydro-1-methylimidazol-2-ylmethyl)[5a-methyl-phenilamo]-methanesulfonate salt, a non-specific alpha adrenergic blocker. Phenelzine mesylate USP is a white to off-white, odorless crystalline powder with a molecular weight of 377.36. It is sparingly soluble in water, soluble in alcohol, and slightly soluble in chloroform. The empirical formula is C_{14}H_{26}N_2O_2S, and the chemical structure is.

Oravense (phenelzine mesylate) Injections is a clear, colorless, sterile, non-pyrogenic, isotonic, preservative-free solution. Each 1.7 ml cartridge contains 0.4 mg phenelzine mesylate, D-mannitol, edetate disodium, and sodium acetate. Either acetic acid or sodium hydroxide is used as necessary to adjust the pH.

12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
The mechanism by which OveraVerse accelerates recovery from soft tissue anesthesia and the associated functional deficits is not fully understood. Phenelzine mesylate, the active ingredient in OveraVerse, produces an alpha-adrenergic block of relatively short duration resulting in vasodilatation when applied to vascular smooth muscle. In an animal model, OveraVerse increased local blood flow in subcutaneous tissue of the dog when given after intracranial injection of lidocaine 2% with 1:100,000 epinephrine.

12.2 Pharmacokinetics
Following OveraVerse administration, phenelzine is 100% available from the subcutaneous injection site and peak concentrations are achieved 10-20 minutes after injection. Phenelzine plasma exposure increased linearly after 0.5 mg compared to 0.4 mg OveraVerse subcutaneous injection. The terminal elimination half-life of phenelzine in the blood was approximately 2-3 hours.

Pediatrics
Following OveraVerse administration, the phenelzine plasma half-life was higher (approximately 3.5-4.6) in children who weighed between 25 and 30 kg (23 and 66 lbs) than in children who weighed more than 30 kg. However, phenelzine AUC was similar between the two groups. It is recommended that in children weighing 15-30 kg, the maximum dose of OveraVerse should be limited to 7.5 cartridges (0.2 mg) (See Dosage and Administration section).

The pharmacokinetics of OveraVerse in adults and in children who weighed more than 30 kg (66 lbs) are similar after intravenous subcutaneous injection.

OveraVerse has not been studied in children under 3 years of age weighing less than 15 kg (33 lbs). The pharmacokinetics of Overaversed after administration of more than 10 cartridges (1 mg) does not have been studied in children.

13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity studies with Oravense have been conducted. Phenelzine was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay. In the in vitro chemoprevention assay in Chinese hamster ovary cells, numerical alterations were slightly increased after a 4-hour exposure without metabolic activation and structural alterations were slightly decreased after a 4-hour exposure to phenelzine without metabolic activation. The metabolically activated form is one of the highest concentrations tested, but neither numerical nor structural alterations were increased after a 24-hour exposure without metabolic activation. Phenelzine was not clastogenic in two in vivo micronucleus assays. At doses up to 150 mg/kg (13.4 times human therapeutic exposure levels at the Cmax, phenelzine mesylate was shown to have no adverse effects on male fertility in the rat.

14. CLINICAL SAFETY AND EFFECTIVENESS OF ORAVENSE when used for reversal of soft tissue anesthesia (STA), i.e., anesthesia of the lips and tongue following a dental procedure that required local anesthesia containing a vasoconstrictor, were evaluated in the following clinical studies. Oravense induced reversal of local anesthetic effects on the teeth, mandible and maxilla has not been assessed.

Two Phase 3, double-blind, randomized, multi-center, controlled studies were conducted in dental patients who had mandibular (Study 1) or maxillary (Study 2) extractions or periodontal maintenance procedures who had received a local anesthetic that contained a vasoconstrictor. The primary endpoint was time to normal lip sensation as measured by patient reported responses to lip palpation. The secondary endpoints included patients' perception of altered function, sensation and appearance, and their actual functional deficits in smiling, speaking, drinking and drooling, as assessed by both the patient and an observer blinded to the treatment. In the mandibular study, the time to recovery of tongue sensation was also a secondary endpoint. Patients were stratified by type and amount of anesthetic administered.

Oravense was administered at a cartridge rate of 1:1 to local anesthetic. The control was a sham injection.

Oravense reduced the median time to recovery of normal sensation in the lower lip by 85 minutes (55%) compared to control. The median time to recovery of normal sensation in the upper lip was reduced by 83 minutes (52%). The differences between these times for both studies are depicted in Kaplan-Meier plots for time to normal lip sensation in.

In Study 1 (mandibular), Oravense accelerated: a) the recovery of the perception of normal appearance and function by 65 minutes (30%), b) the recovery of normal function by 69 minutes (30%), and c) the recovery of normal sensation in the tongue by 65 minutes (51%). In Study 2 (maxillary), the recovery of the perception of normal appearance and function was reduced by 60 minutes (55%) and the recovery of normal function was reduced by 45 minutes (45%).

Study 3, a pediatric, Phase 2, double-blind, randomized, multi-center controlled study was conducted in dental patients who had received 2% lidocaine with 1:100,000 epinephrine. Dental patients (n = 352, ages 4-11 years) received 1/2 cartridge of local anesthetic if they weighed ≥50 kg, or <50 kg, and one-half or one cartridge if they weighed ≥50 kg at a cartridge rate of 1:1 local anesthetic.

The median time to normal lip sensation in patients 6-11 years of age who were treatable in the lip-palpation procedures, for mandibular and maxillary procedures combined, was reduced by 75 minutes (56%). Within 1 hour after administration of Oravense, 44 patients (31%) reported normal lip sensation, while only 9 patients (21%) randomized to the control group reported normal lip sensation. In this study, neither the patients' perception of their appearance or ability to function nor their actual ability to function was evaluated.

16. HOW SUPPLIED/STORAGE AND HANDLING
Oravense (phenelzine mesylate) injection 0.4 mg/1.7 ml is supplied in a dental cartridge, in cartons of 10 and 50 cartridges. Each cartridge is individually packaged in a separate compartment of a 10 cartridge blister pack.

NDC 04293-110-01
NDC 04293-110-02
Storage at controlled room temperature, 20-25°C (68-77°F) with brief excursions permitted between 15-30°C (59-86°F) (see USP Controlled Room Temperature).

Protect from direct heat and light. Do not permit to freeze.

Manufactured by
Novocal Pharmaceutical of Canada, Inc.
Cambridge, Ontario, Canada

For
Novocal Pharmaceuticals, Inc.
San Diego, CA 92120


17. PATIENT COUNSELING INFORMATION
Patients should be instructed not to eat or drink until normal sensation returns.