OraVerse® + + + + ½

Novalar Pharmaceuticals, Inc.  
858.436.1100  
888.888.1441  
www.OraVerse.com

Description

OraVerse is a local anesthesia reversal agent that accelerates the return to normal sensation and function for patients after routine dental procedures. It is a formulation of phentolamine mesylate and is recommended for adults and children age 6 and older and weighing 33 lbs or more. OraVerse is dispensed in a standard dental cartridge marked with a green label for ease of identification. It is administered by injection with a standard dental syringe in the same injection site as that used for the local anesthetic. OraVerse is used in a 1:1 ratio to local anesthetic. Each package includes 10, 1.7mL cartridges and prescribing information. OraVerse was used by 16 consultants in 128 cases. Seventy-five patients responded to surveys. OraVerse received a 93% clinical rating.

Suggested Retail Cost

- $130.00/Box of 10 Cartridges  
  ($13/Cartridge)
- $650.00/Box of 50 Cartridges  
  ($13/Cartridge)

Product Features

Consultants commented that OraVerse was easy to use and effective. Cartridges are well marked to differentiate it from anesthetic. Consultants reported that some patients experienced more

Consultants’ Comments

- “It really works! I found that patients responded very well and loved that the numbness wore off faster than normal.”
- “Patients appreciated having an option to reverse the effects of anesthetic.”
- “I had patients report that the injections sites were more sore, tender and sometimes bruised due to an additional injection.”

Patients’ Comments

- “The best dental invention ever!”
- “Numbness was wearing off within 25 minutes and was totally gone by 35 minutes.”
- “I had less drooling and cheek biting.”
- “I had soreness at the injection site the next day.”
soreness or bruising from the additional injection. Most of the patients responded that numbness wore off quickly - within an hour - and they tolerated OraVerse well. Ninety-three percent of patients surveyed felt that OraVerse was effective at lessening the amount of time they were numb. Eighty-four percent of patients reported that OraVerse improved their dental experience and they would request it again. Seventy-five percent of consultants would continue to use OraVerse in their practice and 94% would recommend it.

Clinical Tips
• Ratio is 1:1 – use one cartridge of OraVerse for each cartridge of anesthetic.

• The maximum recommended dose of OraVerse is two cartridges in patients age 12 or greater, one cartridge in children age 6-11 years and weighing over 66 lbs, and one half cartridge in children 6-11 years and weighing 33 to 66 lbs.
• OraVerse is not indicated in children under 6 years of age or weighing less than 33 lbs.
• Do not use after invasive procedures such as endodontic treatment or surgery, where post-operative discomfort is anticipated.
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.
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 (phenylephrine mesylate) Injection
Initial U.S. Approval: 1992

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 or weighing less than 15 kg (33 lbs). (1)

DOSE AND ADMINISTRATION

<table>
<thead>
<tr>
<th>Amount of Local Anesthetic Administered</th>
<th>Dose of OraVerse</th>
</tr>
</thead>
<tbody>
<tr>
<td>½ Cartridge</td>
<td>0.2 mg</td>
</tr>
<tr>
<td>1 Cartridge</td>
<td>0.4 mg</td>
</tr>
<tr>
<td>2 Cartridges</td>
<td>0.8 mg</td>
</tr>
</tbody>
</table>

OraVerse is administered using the same location(s) and same technique(s) (infiltration or block injection) used for the administration of local anesthetic. [2.1]

FULL PRESCRIBING INFORMATION: CONTENTS*

1. INDICATIONS AND USAGE
OraVerse is indicated for 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 or weighing less than 15 kg (33 lbs). (1)

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 (mg)</th>
<th>Dose of OraVerse (cartridges)</th>
</tr>
</thead>
<tbody>
<tr>
<td>½ Cartridge</td>
<td>0.2</td>
<td>1</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>1</td>
</tr>
</tbody>
</table>

OraVerse should be administered following the dental procedure (using the same location(s) and technique(s) (infiltration 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).

(1) Note: Data in pediatric patients under 6 years of age or 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 10 years of age.

3. DOSAGE FORMS AND STRENGTHS
0.4 mg/1.7 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 intravenous administration of phenylephrine, usually in association with marked hypertensive episodes or shock-like states which occasionally follow parotid resection. Tachycardia and cardiac arrhythmias may occur with the use of phenylephrine or other alpha-adrenergic blocking agents. (5.1)

ADVERSE REACTIONS
The most common adverse reaction with OraVerse (incidence > 3%) is injection-site pain. (5)
To report SUSPECTED ADVERSE REACTIONS, contact Nevirtel at 1-800-888-1401 or FDA at 1-800-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 30 kg (66 lbs), the maximum dose of OraVerse recommended is 1/2 cartridge (0.2 mg). (8.4)

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 1. Adverse Reactions with Frequency Greater Than or Equal to 3% and Equal to or Exceeding Control

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>OraVerse</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N = 418)</td>
<td>535</td>
<td></td>
</tr>
<tr>
<td>0.2 mg (N = 83)</td>
<td>83</td>
<td>N (%)</td>
</tr>
<tr>
<td>0.4 mg (N = 204)</td>
<td>204</td>
<td>N (%)</td>
</tr>
<tr>
<td>0.8 mg (N = 51)</td>
<td>51</td>
<td>N (%)</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 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, fever, swelling, increased blood pressure/hypertension, injection site reactions (jaw pain, oral pain), pruritus, photophobia, urticaria, abdominal pain, and vomiting. The majority of these adverse reactions were mild and resolved within 48 hours. The few reports of photophobia were mild and transient and resolved during the same time period.

6.3 Post Marketing Adverse Reactions from Literature and Other Sources
The following adverse reactions have been identified during postapproval parenteral use of phenylephrine 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 myocardial infarction, cerebrovascular episodes and cardiomyopathy have been reported with the use of phenylephrine. In addition, weakness, diziness, flushing, orthostatic hypotension, and nasal stuffiness have occurred.

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

7.1 Lidoconine and Ephrine
When OraVerse was administered as an intranasal submucosal injection 30 minutes after injection of a local anesthetic, 2% lidocaine with 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 benefit justifies the potential risk to the fetus.

Oral administration of phenylephrine to pregnant rats and mice at doses of at least 24 times the recommended dose (based on a 60 kg human) resulted in slight decreases in growth and slight skeletal immaturity of the fetuses. Immaturity was manifested by increased incidences of incomplete or unossified calvaria and phalangeal nuclei of the hind limbs and of incompletely ossified sternum. At oral phenylephrine doses of at least 60 times the recommended dose (based on a 60 kg human), a slight lower rate of implantation was found in the rat. Phenylephrine does not affect embryonic or fetal development in the rabbit at oral doses of at least 20 times the recommended dose (based on a 60 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 phenylephrine 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 Oraluse. The safety and effectiveness of Oraluse have been established in the age group 6-17 years. Effectiveness in pediatric patients below the age of 6 years has not been established. Use of Oraluse in patients between the ages of 6 and 17 years old is supported by evidence from adequate and well-controlled studies of Oraluse in adults, with additional adequate and well-controlled studies of Oraluse in pediatric patients ages 12-17 years old (Studies 1 (mandibular procedure) and 2 (maxillary procedure)) and ages 6-11 years old (Study 3 (mandibular and maxillary procedures)). The safety, but not the efficacy, of Oraluse has been evaluated in pediatric patients under the age of 6 years old. Dosages in pediatric patients may need to be limited based on body weight. (See Dosage and Administration 2)

8.5 Geriatric use The overall number of patients in clinical trials of Oraluse, 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. Overdose with parenterally administered phenelzine is characterized chiefly by cardiovascular disturbances, such as arrhythmias, hypotension, and possibly shock. In addition, the following might occur: excitation, headache, sweating, paresthesia, tachycardia, tachypnea, palpitations, somnolence, tremor, diaphoresis, hyperglycemia, and cyanosis.

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 a phenylalanine, 1-(3,5-dimethoxy-4-(3-methyl-phenylamino)-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 377.48. It is sparingly soluble in water, soluble in alcohol, and slightly soluble in chloroform. The empirical formula is C_{28}H_{30}N_{10}O_{5}S, and the chemical structure is as follows:

![Chemical Structure]

12. CLINICAL PHARMACOLOGY

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

12.2 Pharmacokinetics Following Oraluse administration, phenelzine is 100% available from the subcutaneous injection site and peak concentrations are achieved 15-20 minutes after injection. Phenelzine plasma exposure increased linearly after 0.5 mg compared to 0.4 mg Oraluse subcutaneous injection. The terminal elimination half-life of phenelzine in the blood was approximately 2-3 hours.

12.3 Pharmacodynamics Following Oraluse administration, the phenelzine plasma concentration was higher in children who weighed between 15 and 30 kg (33-66 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 Oraluse be limited to 1 cartridge (0.2 mg) (See Dosage and Administration section).

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

Oraluse has not been studied in children under 3 years of age weighing less than 15 kg (33 lbs). The pharmacokinetics of Oraluse after administration of more than 1 cartridge (1 mg) has not been studied in children.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity studies with phenelzine have not been conducted.

Phenelzine was not mutagenic in the in-vitro bacterial reverse mutation assay (Ames) assay. In the in-vivo chromosomal aberration study in Chinese hamster ovary cells, numerical aberrations were slightly increased after a 4-hour exposure to phenelzine with and without metabolic activation. Structural aberrations were slightly increased after a 4-hour exposure to phenelzine with metabolic activation at all of the highest concentrations tested, but none of the structural aberrations were increased after a 24-hour exposure without metabolic activation. Phenelzine was not clastogenic in two in-vivo mouse micronucleus assays. At doses up to 150 mg/kg (0.25 times human therapeutic exposure levels at the Cmax, phenelzine mesylate was shown to have no adverse effects on female rat in the rat.

14. CLINICAL SAFETY AND EFFECTIVENESS

14.1 The safety and efficacy of Oraluse were evaluated in several clinical studies. Oraluse 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) restorative, endodontic, or periodontal maintenance procedures and 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 chewing, 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.

Oraluse was administered at a cartilage ratio of 2:1 to local anesthetic. This was a single blind study.

Oraluse reduced the median time to recovery of normal sensation in the lower lip by 15 minutes (55%) compared to control. The median time to recovery of normal sensation in the upper lip was reduced by 83 minutes (55%). The differences between these times for both studies are depicted in Kaplan-Meier plots for time to normal lip sensation in Figures 1 and 2. Within 1 hour after administration of Oraluse, 41% of patients reported normal lower lip sensation as compared to 7% in the control group, and 59% of patients in the Oraluse group reported normal upper lip sensation as compared to 12% in the control group.

Figure 1: Kaplan-Meier Plot of Time to Recovery of Normal Sensation in the Lower Lip (ITT Analysis Data Set)

![Kaplan-Meier Plot]

Figure 2: Kaplan-Meier Plot of Time to Recovery of Normal Sensation in the Upper Lip (ITT Analysis Data Set)

![Kaplan-Meier Plot]

In Study 1 (mandibular), Oraluse accelerated: a) the recovery of the perception of normal appearance and function by 15 minutes (55%), b) the recovery of normal function by 15 minutes (59%), and c) the recovery of normal sensation in the tongue by 65 minutes (59%). In Study 2 (maxillary), the recovery of the perception of normal appearance and function was reduced by 60 minutes (58%) and the recovery of normal function was reduced by 48 minutes (57%).

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 (6 to 11 years old) received 1/2 cartridge of local anesthetic if they weighed 30 kg or less, and one-half or one full cartridge if they weighed 30 kg or more. All patients received Oraluse 0.2 mg (0.4 mg). The median time to normal lip sensation in patients 6 to 11 years of age who were sleepable in the lip palpation procedures, for mandibular and maxillary procedures combined, was reduced by 75 minutes (55%). Within 1 hour after administration of Oraluse, 44 patients (93%) reported normal lip sensation, while only 10 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 Oraluse (phenelzine mesylate) injection 0.4 mg/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 5 cartridge blister pack.

NDC: 0593-110-02
NDC: 0593-120-02

Store 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 Novocapharmaceuticals of Canada, Inc.
Cambridge, Ontario, Canada
For Novocapharmaceuticals, Inc.
San Diego, CA 92120

US Patent Nos. 6,764,670, 6,872,380, 7,229,620
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17. PATIENT COUNSELING INFORMATION Patients should be instructed not to eat or drink until normal sensation returns.

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