OraVerse™

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 Draft Date: April 2016

---INDICATIONS AND USAGE---

OraVerse an alpha adrenergic blocker, is indicated for adult and pediatric patients ages 3 years and older for the reversal of soft-tissue anesthesia, i.e., anesthesia of the lip and tongue, and the associated functional deficits resulting from an intralabial submucosal injection of a local anesthetic containing a vasoconstrictor. (1)

---DOZING AND ADMINISTRATION---

Amount of Local Anesthetic Administered

<table>
<thead>
<tr>
<th>Cartridge(s)</th>
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<td>0.4 mg</td>
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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)

---DOSE FORM AND STRENGTH---

0.4 mg/1.7 mL solution per cartridge (3)

---CONTRAINDICATIONS---

OraVerse is contraindicated in individuals with:

- Hypersensitivity to the active substance or to any ingredients in the formulation. (4)

---WARNINGS AND PRECAUTIONS---

Myocardial infarction, cerebrovascular spasm, and cerebrovascular occlusion have been reported to occur following the intravenous or intramuscular administration of phentolamine, usually in association with marked hypotensive episodes or other-like states which occasionally require 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 of OraVerse (incidence >5% and > control) is injection-site pain. (6)

---USE IN SPECIFIC POPULATIONS---

* Use in pediatric patients under 3 years of age or weighing less than 15 kg (33 lbs) is not recommended.

---DRUG INTERACTIONS---

1. INDICATIONS AND USAGE

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.

2.2 Dosing in Special Populations

---CONTRAINDICATIONS---

OraVerse should be administered following the dental procedure using the same location(s)

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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 45 hours. There were no serious adverse reactions and no discontinuations due to adverse reactions.

Table 1: Adverse reactions where the frequency was greater than or equal to 3% in any OraVerse dose group was equal to or exceeded that of the control group.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>OraVerse</th>
<th>Control</th>
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<tbody>
<tr>
<td>Pruritus</td>
<td>117 (28)</td>
<td>96 (27)</td>
</tr>
<tr>
<td>Rash</td>
<td>7 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Headache</td>
<td>20 (39)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>25 (6)</td>
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</tr>
<tr>
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</tr>
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<td>418 (100)</td>
<td>359 (100)</td>
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12. CLINICAL PHARMACOLOGY

Sodium acetate. Either acetic acid or sodium hydroxide is used as necessary to adjust the pH.

8.2 Lactation

Type and amount of anesthetic administered. OraVerse was administered at a cartridge ratio of 1:1 to local anesthetic.

8.4 Pediatric Use

The safety and efficacy of OraVerse has not been established in patients younger than 3 years.

The safety and effectiveness of OraVerse in pediatric patients ages 3 years and older is supported by evidence from adequate and well-controlled studies of OraVerse in adults, with additional adequate and well-controlled studies of OraVerse in pediatric patients ages 12 to 17 years old. Studies 1 (mandibular procedures) and 2 (maxillary procedures), ages 6 to 11 years old, Study 3 (mandibular and maxillary procedures), and Study 4 (oral surgery) were conducted in dental patients who had received 2% lidocaine with 1:100,000 epinephrine. Dental patients (n=152, ages 4-11 years) received 1/2 cartridge of OraVerse if they weighed ≥15 kg but <30 kg, and one-half or one full cartridge if they weighed ≥30 kg at a cartridge ratio of 1:1 to local anesthetic.

10. OVERDOSAGE

No deaths due to acute poisoning with phentolamine have been reported. Overdose with parenterally administered phentolamine is characterized chiefly by cardiovascular disturbances, such as arrhythmias, tachycardia, hypotension, and possibly shock. In addition, the following might occur: excitement, headache, sweating, pulmonary contraction, visual disturbances, nausea, vomiting, diarrhea, or hypoglycemia.

11. DESCRIPTION

Phentolamine mesylate is a white to off-white crystalline powder with a molecular weight of 377.46. It is sparingly soluble in water, soluble in alcohol, and slightly soluble in chloroform.

The empirical formulation is C17H19N3O•CH403S, and the chemical structure is:

\[
\text{C17H19N3O•CH403S} \quad \text{[salt]} \quad \text{a non-specific alpha adrenergic blocker.}
\]

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Following OraVerse administration, phentolamine is 100% available from the submucosal injection site and peak concentrations are achieved 10-20 minutes after injection. Phentolamine systemic exposure increased linearly after 0.8 mg compared to 0.4 mg OraVerse submucosal injection. The terminal elimination half-life of phentolamine in the blood was approximately 2.3 hours.

13. NONCLINICAL TOXICITY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenic studies with OraVerse have not been conducted.

Mutagenesis

Phentolamine was not mutagenic in the in-vitro bacterial reverse mutation (Ames) assay. In the in-vitro micronucleus test, rabbit testes were slightly increased after a 4-hour exposure to phentolamine without metabolic activation and structural aberrations were slightly increased after a 4-hour exposure to phentolamine with metabolic activation only at the highest concentrations tested, but neither numerical nor structural aberrations were increased after a 20-hour exposure without metabolic activation. Phentolamine was not clastogenic in two in vivo mouse micronucleus assays.

Impairment of Fertility

The effect of phentolamine on female fertility has not been studied. Male rats treated with oral phentolamine mesylate were not affected on fertility (5 weeks after mid-cycle). During the period of treatment (6 weeks after mating) were mated with untreated females. At doses up to 143-times human therapeutic exposure levels at the Cmax, no adverse effect on fertility parameters in the untreated females mated with the treated males was observed.

14. CLINICAL STUDIES

The safety and efficacy of OraVerse 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. OraVerse-induced reversal was compared to sham injection, i.e., a needle injection with no pharmacologic agent into the recovery of the perception of normal appearance and function was reduced by 60 minutes (40%), b) the recovery of normal function by 65 minutes (50%), and c) the recovery of normal sensation in the tongue by 65 minutes (52%). In Study 2 (maxillary), the recovery of the perception of normal appearance and function was reduced by 60 minutes (50%) and the recovery of normal function was reduced by 45 minutes (43%). 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=152, ages 4-11 years) received 1/2 cartridge of OraVerse if they weighed ≥15 kg but <30 kg, and one-half or one full cartridge if they weighed ≥30 kg at a cartridge ratio of 1:1 to local anesthetic.

The median time to normal lip sensation in patients 6 to 11 years of age who were trainable in the lip-palpation procedure, for mandibular and maxillary procedures combined, was reduced by 75 minutes (56%). Within 1 hour after administration of OraVerse, 44 patients (61%) reported normal lip sensation, while 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.

Study 4, a pediatric, Phase 4, double-blind, randomized, multi-center, controlled study was conducted in dental patients undergoing mandibular and maxillary procedures after receiving 2% lidocaine with 1:100,000 epinephrine. Patients 2.5 years of age received sham injection (n=51) or 1/4 cartridge of OraVerse if they weighed ≥10 kg but <15 kg (n=5), 1/2 cartridge if they weighed ≥15 kg but <30 kg (n=91), and a full cartridge if they weighed ≥30 kg (n=3). This study was not designed to demonstrate efficacy.

The median time to normal lip sensation in patients 4 and 5 years of age who were trainable in the lip-palpation procedure, for mandibular and maxillary procedures combined, was reduced by 48 minutes (44%). Within 2 hours after administration of OraVerse, 57 patients (80%) reported normal lip sensation, while 9 patients (15%) randomized to the sham injection group reported normal lip sensation. There were no significant differences between OraVerse and sham injection for time to normal lip sensation. The median time to assessment battery and time to recovery of normal tongue sensation (for mandibular procedures only).

16. HOW SUPPLIED STORAGE AND HANDLING

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

17. PATIENT COUNSELING INFORMATION

OraVerse reduced the median time to recovery of normal sensation in the lower lip by 85 minutes (56%) compared to control in the treatment group and 59% of patients in the OraVerse 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

Figure 2: Kaplan-Meier Plot of Time to Recovery of Normal Sensation in the Upper Lip