***OraVerse*: Reverses Numbness After Dental Procedures**

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Abstract The lingering numbness that can last anywhere from 3 to 5 h after a routine dental procedure is often an unnecessary, inconvenient hassle. Patients may find that their ability to speak, smile, eat and drink is impaired, and may even have uncontrollable drooling. The effects of local dental *anesthetics* can now be reversed. That's because *OraVerse*, an anesthetic reversal agent, can return the patient to normal sensation and function in about half the time. *OraVerse* which is U.S. Food and Drug Administration approved is a safe and effective form of *phentolamine mesylate*, a vasodilator that has been used in several other medical applications since 1952. *OraVerse* injection – the first and only proven safe and effective product of its kind can quickly reverse the effects of local dental anesthetics, so patient can carry on without impairment of talk, smile and drink after dental procedures. Studies also have shown that there are no known drug interactions and no evident toxicity or contraindications for using *OraVerse*.

Keywords *OraVerse* · Submucosal injection · Anaesthesia · Periodontal maintenance · Reverses numbness

Introduction

Patients can have their dental work performed in a pain-free fashion. Of course, the problem with dental anesthetics is that for some people, it takes hours for their mouths to recover from the numbing effect. This issue often translates into a problem for busy working people who can't afford to spend half a day feeling numb in the face. Instead of a quick morning filling appointment being a simple affair, it can negatively impact a person's work performance by impairing speech and impeding a person's ability to present them publicly without humiliation. Fortunately, mouth-related numbness doesn't have to be an all-day affair thanks to a new anesthetic reversal agent called *OraVerse*.

So what is this magic drug and how does it work? *OraVerse* is the first and only local dental anesthesia reversal agent in the market proven to accelerate the reversal of anaesthetic effect (numbness) after dental procedures. To administer *OraVerse*, dentist will inject it into the area of the patient's mouth that has been worked on and is therefore already numb. Since the oral injection site will already be numb by the time the *OraVerse* is given, patients won't feel any additional discomfort during this process. After *OraVerse* is given, patients can expect their numbness recovery period to be virtually reduced to half the duration of total anaesthesia.

OraVerse is recommended for adults, adolescents, and children who are aged six and older and who weigh a minimum of 33 pound.

Description

OraVerse is a formulation of *phentolamine mesylate* that accelerates the return to normal sensation and function for patients after routine dental procedures. *OraVerse* is

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Fig. 1 Photomicrograph of normal (n) and degenerated nerve (d) adjacent in the gingival biopsy from an animal 24 hours after it received 27 μ g/kg phentolamine mesylate in the right maxilla adjacent to the first premolar

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, 1.7 ml cartridges and prescribing information [1]. 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 33–66 lbs. *OraVerse* is not indicated in children less than 6 years of age or weighing less than 33 lbs. It is not recommended to use after invasive procedures such as endodontic treatment or surgery, where post-operative discomfort is anticipated [1].

OraVerse increases the diameter of blood vessels in the area. The increase in blood flow removes the extra drug and takes it to the liver and the kidneys to be broken down. Microscopic picture is shown in Fig. [1] [2].

Full Prescribing Information

Indications and Usage: [3, 4]

(1). *OraVerse* is indicated for reversal of the soft-tissue anesthesia (STA), i.e., anesthesia of the lip and tongue, and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor. (2). Prevention or control of hypertensive episodes in patients with *pheochromocytoma*. (3). Pharmacologic test for *pheochromocytoma* (not method of choice). (4). Prevention and treatment of dermal necrosis and sloughing following IV administration or extravasation of *norepinephrine*.

Contraindications

(1). *OraVerse* is not recommended for use in children less than 6 years of age or weighing less than 15 kg. (2). Hypersensitivity to *phentolamine* or related compounds. (3). History of *myocardial infarction*, *coronary insufficiency*, *angina*, or other evidence suggestive of *coronary artery disease*

Dosage and Administration

General Dosing Information: [5]

The recommended dose of *OraVerse* is based on the number of cartridges of local anesthetic with *vasoconstrictor* administered:

Amount of local anesthesia administered	Dose of <i>OraVerse</i> (mg)	Dose of <i>OraVerse</i> (Cartridge)
1/2 cartridge	0.2	1/2
1 cartridge	0.4	1
2 cartridge	0.8	2

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.

If dose is effective, normal skin color should return to the blanched area within 1 h

Vasoconstrictor (*alpha-adrenergic agonist*) extravasation: Infiltrate the area of extravasation with multiple small injections using only 27 or 30 gauge needles and changing the needle between each skin entry. Be careful not to cause so much swelling of the extremity or digit that a *compartment syndrome* occurs. If infiltration is severe, may also need to consult vascular surgeon.

Dosing in Special Populations

In pediatric patients weighing 15–30 kg, the maximum dose of *OraVerse* recommended is 1/2 cartridge (0.2 mg).

(Note: Use 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 12 years of age).

Dosage Forms and Strengths

0.4 mg/1.7 ml solution per cartridge.

Warnings and Precautions

Cardiovascular Events

Myocardial infarction, cerebrovascular spasm, and cerebrovascular occlusion have been reported to occur following the parenteral administration of *phentolamine*. These events usually occurred in association with marked *hypotensive* episodes producing shock-like states. *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

Cardiovascular

Tachycardia (6%); *bradycardia* (4%); acute and prolonged *hypotensive episodes*, *cardiac arrhythmias*, *orthostatic hypotension* (post marketing).

Miscellaneous

Post procedural pain (10%); injection-site pain (6%).

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

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 0.2, 0.4 or 0.8 mg of *OraVerse*. The majority of adverse reactions

were mild and resolved within 48 h. There were no serious adverse reactions and no discontinuations due to adverse reactions [7].

Table 1 lists adverse reactions where the frequency was greater than or equal to 3% in any *OraVerse* dose group and was equal to or exceeded that of the control group [3].

An examination of population subgroups did not reveal a differential adverse reaction incidence 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 [Fig. 2, 3].

Adverse Reactions in Clinical Trials

Adverse reactions reported by less than 3% but at least two dental patients receiving *OraVerse* and occurring at a greater incidence than those receiving control, included *diarrhea*, *facial swelling*, *increased blood pressure/hypertension*, injection site reactions, jaw pain, oral pain, *paresthesia*, *pruritis*, *tenderness*, *upper abdominal pain* and *vomiting*. The majority of these adverse reactions were mild and resolved within 48 h. The few reports of *paresthesia* were mild and transient and resolved during the same time period [8].

Post Marketing Adverse Reaction Reports from Literature and Other Sources

The following adverse reactions have been identified during post approval *parenteral* 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.

Table 1 Adverse reaction with frequency greater than or equal to 3% and equal to or exceeding control [3]

Adverse Event	<i>OraVerse</i>				Control
	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 (%)
Patients with AE _x	15 (18)	82 (29)	20 (39)	117 (28)	96 (27)
Tachycardia	0 (0)	17 (6)	2 (4)	19 (5)	20 (6)
Bradycardia	0 (0)	5 (2)	2 (4)	7 (2)	1 (0.3)
Injection site pain	5 (6)	15 (5)	2 (4)	22 (5)	14 (4)
Post procedural pain	3 (4)	17 (6)	5 (10)	25 (6)	23 (6)
Headache	0 (0)	10 (4)	3 (6)	13 (3)	14 (4)

Fig. 2 Kaplan-Meier plot of time to recovery of normal sensation in the lower lip (ITT analysis data set)

Fig. 3 Kaplan-Meier plot of time to recovery of normal sensation in the upper lip (ITT analysis data set)

Acute and prolonged *hypotensive* episodes and *cardiac arrhythmias* have been reported with the use of *phentolamine*. In addition, weakness, *dizziness*, *flushing*, *orthostatic hypotension*, and *nasal stuffiness* have occurred [9].

Drug Interactions

Antihypertensive Agents

Withhold prior to test for diagnosis of *pheochromocytoma*; do not perform this test on *normotensive patients* [4].

Epinephrine, Ephedrine

Vasoconstrictive and *hypertensive* effects of *epinephrine* and *ephedrine* are antagonized by *phentolamine* [10].

Lidocaine and Epinephrine

When *OraVerse* was administered as an *intraoral submucosal* injection 30 min after injection of a local anesthetic, 2% *lidocaine HCl* with 1:100,000 *epinephrine*, the *lidocaine* concentration increased immediately after *OraVerse* intraoral injection. *Lidocaine*, Area under the concentration Curve (AUC) and *Cmax* (maximum drug concentration achieved in systemic circulation following drug administration) values were not affected by administration of *OraVerse*. *OraVerse* administration did not affect the *Pharmaco Kinetics (PK)* of *epinephrine* [11].

Laboratory Test Interactions

There are no known drug interactions with *OraVerse*.

Uses in Specific Populations

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 *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 calcaneal* and *phalangeal nuclei* of the hind limb and of incompletely *ossified sternbrae*. At oral *phentolamine* doses at least 60 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 60 kg human). No *teratogenic* or *embryotoxic* effects were observed in the rat, mouse, or rabbit studies [12].

Nursing Mothers

It is not known whether *OraVerse* is secreted in human milk. Because many drugs are secreted 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.

Pediatric Use

In clinical studies, pediatric patients between the ages of 3 and 17 years received *OraVerse*. The safety and effectiveness of *OraVerse* 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 *OraVerse* in patients between the ages of 6 and 17 years old 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 aged 12–17 years old [studies 1 (mandibular procedures) and 2 (maxillary procedures)] and ages 6–11 years old [study 3 (mandibular and maxillary procedures)]. The safety, but not the efficacy, of *OraVerse* 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 [13].

Geriatric Use

Of the total number of patients in clinical studies of *OraVerse*, 55 were 65 and over, while 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.

Overdosage

No deaths due to acute poisoning with *phentolamine* have been reported [14].

Overdosage with *parenterally* administered *phentolamine* is characterized chiefly by cardiovascular disturbances, such as *arrhythmias*, *tachycardia*, *hypotension*, and possibly *shock*. In addition, the following might occur: *excitation*, *headache*, *sweating*, *pupillary constriction*, *visual disturbances*, *nausea*, *vomiting*, *diarrhea*, or *hypoglycemia*.

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 [15].

Chemical Structure

Phentolamine mesylate is phenol, 3-[[[4, 5-dihydro-1 H-imidazol-2-yl) methyl] (4-methyl-phenyl)amino]-, methanesulfonate (salt), a non-specific alpha adrenergic blocker.

Phentolamine mesylate United States Pharmacopoeia (USP) is a white to off-white, odorless 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 $C_{17}H_{19}N_3O \cdot CH_4O_3S$ and the chemical structure is [3].

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 [3].

Clinical Pharmacology

Mechanism of Action

The mechanism by which *OraVerse* accelerates reversal of STA 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 *vasodilatation* 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 *intra oral injection* of *lidocaine* 2% with 1:100,000 *epinephrine*.

Pharmacokinetics: [16]

Following *OraVerse* administration, *phentolamine* is 100% available from the *submucosal* injection site and peak concentrations are achieved 10–20 min after injection. *Phentolamine* systemic exposure increased linearly after 0.8 mg compared to 0.4 mg *OraVerse* *intraoral submucosal* injection. The terminal elimination half-life of *phentolamine* in the blood was approximately 2–3 h [16].

Absorption

T max (Time required to achieve maximum drug concentration in systemic circulation) is 10–20 min.

Elimination

Urine (13% as unchanged drug). Half-life is 19 min (IV) and 2–3 h.

Pediatrics

Following *OraVerse* administration, the *phentolamine C_{max}* (maximum drug concentration achieved in systemic circulation following drug administration) was higher (approximately 3.5-fold) in children who weighed between 15 and 30 kg (33 and 66 lbs) than in children who weighed more than 30 kg. However, *phentolamine AUC* was similar between the two groups. It is recommended that in children weighing 15–30 kg, the maximum dose of *OraVerse* should be limited to ½ cartridge (0.2 mg).

The *pharmacokinetics* of *OraVerse* in adults and in children who weighed more than 30 kg (66 lbs) is similar after *intraoral submucosal* injection.

OraVerse has not been studied in children under 3 years of age or weighing less than 15 kg (33 lbs). The *pharmacokinetics* of *OraVerse* after administration of more than 1 cartridge (0.4 mg) has not been studied in children [13].

Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with *OraVerse* have not been conducted.

Phentolamine was not *mutagenic* in the *in vitro* bacterial reverse mutation (Ames) assay. In the *in vitro* chromosomal aberration study in Chinese hamster *ovary* cells, numerical aberrations were slightly increased after a 4 h exposure to *phentolamine* without metabolic activation and structural aberrations were slightly increased after a 4 h exposure to *phentolamine* with metabolic activation only at the highest concentrations tested, but neither numerical nor structural aberrations were increased after a 20 h exposure without metabolic activation. *Phentolamine* was not *clastogenic* in two *in vivo* mouse micronucleus assays. At doses up to 150 mg/kg (143 times human therapeutic exposure levels at the *C_{max}*), *phentolamine mesylate* was shown to have no adverse effects on male *fertility* in the rat [17].

Clinical Studies

The safety and efficacy of *OraVerse* when used for reversal of STA, were evaluated in the following clinical studies. The efficacy of *OraVerse* on reversal of local anesthesia of the teeth, mandible and maxilla has not been assessed.

Two Phases 3, double-blinded, randomized, multi-center, controlled studies were conducted in dental patients who had mandibular (study 1) or maxillary (study 2) restorative 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 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. *OraVerse* was administered at a cartridge ratio of 1:1 to local anesthetic. The control was a *sham* injection [12].

OraVerse reduced the *median time* to recovery of normal sensation in the lower lip by 85 min (55%) compared to control. The median time to recovery of normal sensation in the upper lip was reduced by 83 min (62%). The

differences between these times for both studies are depicted in *Kaplan–Meier plots* for time to normal lip sensation in Figs. 2 and 3. Within 1 h after administration of *OraVerse*, 41% of patients reported normal lower lip sensation as compared to 7% in the control group, and 59% of patients in the *OraVerse* group reported normal upper lip sensation as compared to 12% in the control group [12].

In study 1 (mandibular), *OraVerse* accelerated: a) the recovery of the perception of normal appearance and function by 60 min (40%), b) the recovery of normal function by 60 (50%) min, and c) the recovery of normal sensation in the tongue by 65 min (52%). In study 2 (maxillary), the recovery of the perception of normal appearance and function was reduced by 60 min (50%) and the recovery of normal function was reduced by 45 min (43%) [Fig. 2, 3] [12].

Another study which was, a pediatric, phase 2, double-blinded, randomized, multi-center, controlled study, 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 local anesthetic 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 [12].

The median time to normal lip sensation in patients 6–11 years of age who were trainable in the lip-palpation procedures, for mandibular and maxillary procedures combined, was reduced by 75 min (56%). Within 1 h after administration of *OraVerse*, 44 patients (61%) reported normal lip sensation, while only nine 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 or their actual ability to function was evaluated [12, 18].

Supplied/Storage and Handling

OraVerse (*phentolamine 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.

Store at controlled room temperature, 20–25°C (68–77°F) with brief excursions permitted between 15–30°C (59–86°F). Protect from direct heat and light. Do not permit to freeze [3].

Screening Tests

Urinary assays of *catecholamines* or other biochemical assays have largely supplanted *phentolamine* and other pharmacologic tests for *pheochromocytoma*. *Phentolamine* is usually used as confirmation. Follow specific guidelines for use of *phentolamine*.

Patient Counseling Information

- Patients should be instructed not to eat or drink until normal sensation return. Instruct patient to avoid sudden position changes to prevent *orthostatic hypotension*.
- Instruct patient to notify health care provider if chest pain develops during infusion.
- Advise patient to report the following symptoms to health care provider: *dizziness*, *fainting spells*, or weaknesses.

Important Safety Information

Following *parenteral* use of *phentolamine* at doses between 5 to 15 times higher than the recommended dose of *OraVerse* (*phentolamine mesylate*), *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*, *bradycardia*, 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* [7, 19, 20].

OraVerse (solution for injection/dental cartridge) is administered as a *submucosal* injection and is not to be confused with *phentolamine* used as an intramuscular or intravenous injection for the treatment of *hypertension* associated with *pheochromocytoma* [11].

Conclusion

OraVerse represents a break-through in dentistry that can free patients from the unwanted and unnecessary numb sensation typically experienced after routine dental procedures.

A great benefit that children (and their parents) will experience with *OraVerse* is that their tendency to chew their tongue, cheeks and/or lips when those areas are numb is greatly reduced, and there is less likely to be a problem because the anesthetized area is more quickly returned to normal.

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