PRODUCT MONOGRAPH

[Pr]ORAVERSE
Phentolamine Mesylate Injection House Standard
Phentolamine Mesylate Injection, 0.4mg/1.7mL

Alpha-adrenoreceptor blocker
For Intraoral Submucosal Injection Only

Sponsor:	Manufacturer:	**Date of Preparation:**
Septodont SAS	Novocol Pharmaceutical of Canada, Inc.	**February 24, 2014**
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Submission Control No: 157450

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OraVerse
Phentolamine Mesylate Injection House Standard

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Non-medicinal Ingredients
Intraoral Submucosal Injection	Sterile Solution for Injection Phentolamine Mesylate: 0.4mg/1.7mL (0.235 mg/mL)	Edetate Disodium, Mannitol, Sodium Acetate, Water for Injection, Acetic Acid or Sodium Hydroxide

INDICATIONS AND CLINICAL USE

Adults: OraVerse (phentolamine mesylate) is indicated for reversal of soft-tissue anesthesia resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor, following a non-invasive routine dental procedure.

Pediatrics (6 to 18 years of age): OraVerse is indicated for reversal of soft-tissue anesthesia resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor, following a non-invasive routine dental procedure.

Pediatrics (<6 years of age): Safety and efficacy of OraVerse have not been established in children less than 6 years of age or weighing less than 15 kg (33 lbs). Therefore, OraVerse is not recommended for use in this population (See WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

CONTRAINDICATIONS

OraVerse is contraindicated in patients with:

- Hypersensitivity to the active substance or to any ingredients in the formulation

WARNINGS AND PRECAUTIONS

General

Patients should be instructed not to eat or drink until normal oral sensation returns. Patients should be advised that OraVerse will accelerate the return of normal lip sensation and therefore can increase oral pain.

Use of OraVerse is not recommended in patients undergoing complex dental procedures where post-procedural pain or haemorrhage is anticipated. There are limited data on the use of OraVerse in patients at increased risk of bleeding, including patients treated with anticoagulants.

Caution should be exercised when using OraVerse in such patients due to the increased risk of injection site haemorrhage.

Cardiovascular

Myocardial infraction, cerebrovascular spasm, and cerebrovascular occlusion, usually in association with marked hypotensive episodes, have been reported following parenteral administration of phentolamine mesylate.

As hypotension, tachycardia and cardiac arrhythmias may occur with the use of phentolamine and other alpha-adrenergic blocking agents, clinicians should be alert to the signs and symptoms of these events, particularly in patients with a prior history of cardiovascular disease. OraVerse is not recommended in patients with clinically significant cardiovascular disease.

Special Populations

Pregnant Women:
OraVerse is not recommended for use during pregnancy (See TOXICOLOGY).

Nursing Women:
It is not known whether OraVerse is excreted in human milk. Because of the unknown risks for the breastfeeding infant, OraVerse is not recommended in nursing women.

Pediatrics:
Safety and efficacy of OraVerse have not been established in children less than 6 years of age or weighing less than 15 kg (33 lbs). The safety and efficacy of OraVerse have been established in the age group 6-18 years. Dosages in pediatric patients need to be limited based on body weight (see DOSAGE AND ADMINISTRATION).

Geriatrics:
In the clinical studies of OraVerse, 39 patients were 65 -74 years while 16 patients were older than 75 years. No overall differences in safety or efficacy were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In clinical trials, the most common adverse events with OraVerse that were greater than the sham or placebo group included injection site pain and post procedural pain. The majority of adverse events were mild or moderate and resolved within 48 hours. There were no serious adverse events.

Clinical Trial Adverse Drug Reaction

> *Because clinical trials are conducted under very specific conditions the adverse event rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another*

drug. Adverse event information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of OraVerse was evaluated in 4 studies where dental patients were enrolled including 387 phentolamine-treated patients and 342 sham or placebo-treated patients. In the OraVerse group, 265 patients (68.5%) were administered a dose of 0.4 mg, 74 (19.1%) received 0.2 mg, and 48 (12.4%) received 0.8 mg. Pediatric patients weighting more than 15 kg and less than 30 kg received 0.2 mg, while patients weighting more than 30 kg received either 0.2 mg or 0.4 mg of OraVerse. Adults were administered either 0.4 mg or 0.8 mg of OraVerse.

The treatment-emergent adverse events (TEAE frequency ≥1% and equal or greater than in the sham or placebo group) are listed in Table 1.

The majority of these AEs were mild to moderate and resolved at the end of the observation or follow-up period. The most frequently reported TEAEs were injection site pain, post-procedural pain, tachycardia, bradycardia, and headache.

Table 1. TEAEs with a frequency ≥1% and equal or greater than in the sham or placebo group

	OraVerse			**Sham or placebo**
	0.2 mg (N=74)	**0.4 mg (N=265)**	**0.8 mg (N=48)**	**Total (N=342)**
	N (19.1%)	**N (68.5%)**	**N (12.4%)**	**N (%)**
Injection site pain	5(6.6)	22(8.3)	3(6.3)	15(4.4)
Post procedural pain	3(4.1)	14(5.3)	5(10.4)	23(6.7)
Tachycardia	0 (0.0)	8(3.0)	3(6.3)	8(2.3)
Headache	0 (0.0)	8(3.0)	2(4.2)	8(2.3)
Bradycardia	0 (0.0)	3(1.1)	2(4.2)	2(0.6)
Hypertension	0 (0.0)	4(1.5)	0 (0.0)	1(0.3)
Oral pain	2(2.7)	0(0.0)	1(2.1)	1(0.3)
Increased blood pressure	3(4.1)	1(0.4)	0(0.0)	2(0.6)

Pediatric Patients (4-18 years of age)

In dental patients between the age of 4 and 17 (OraVerse, N = 135; control, N = 96), the more frequent TEAEs consisted of injection site pain, tachycardia, bradycardia, increased blood pressure, and oral pain. There were 25 children aged between 4 to 6 years.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The less common adverse events were: abdominal pain upper, aphthous stomatitis, cold sweat, cough increased, diarrhea, dry mouth, facial pain/swelling, haemorrhage, injection site reaction (i.e. blanching, bruising, gingival erythema, hematoma, paranasal soft tissue swelling, swelling, tenderness in cheek), lacrimation increased, mouth ulceration, nasal congestion, nausea, ocular hyperaemia, open wound, paranasal sinus hypersecretion, peripheral edema, petechia, pharyngolaryngeal pain, pruritus, pyrexia, tongue disorder, tremor, and viral infection.

Post Marketing Adverse Reactions

The following more severe adverse events have been identified during post approval parenteral use of phentolamine mesylate: Acute and prolonged hypotensive episodes and cardiac arrhythmias have been reported.

With OraVerse, weakness, dizziness, flushing, orthostatic hypotension, nasal stuffiness, trismus, nerve injury, burning sensation and hematoma have been reported.

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.

DRUG INTERACTIONS

Overview

OraVerse may augment the hypotensive effect of other antihypertensive agents. Antipsychotics may enhance the hypotensive effect of α-adrenergic blocking agents.

Drug-Drug Interactions

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

Drug-Food Interactions

Patients should be advised not to eat or drink until normal oral sensation returns following the administration of OraVerse.

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Tests Interactions

Interactions with laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

OraVerse may be administered following the administration of the local anesthetic that contains a vasoconstrictor such as epinephrine. Following a routine dental procedure, OraVerse should be administered 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.

Recommended Dose and Dosage Adjustment

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

Amount of Local Anesthetic Administered	Dose of Phentolamine Mesylate
½ cartridge	0.2 mg (½ cartridge)
1 cartridge	0.4 mg (1 cartridge)
2 cartridges	0.8 mg (2 cartridges)

Adults:
The maximum recommended dose is 0.8 mg (2 cartridges).

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

Use in pediatric patients under 6 years of age or weighing less than15 kg (33 lbs) is not recommended. A dose of more than 0.4 mg (1 cartridge) of OraVerse has not been studied in children less than 18 years of age.

Patients with hepatic impairment:
OraVerse has not been studied in patients with hepatic impairment. Since phentolamine is metabolized principally in the liver, OraVerse should be used with caution in patients with hepatic impairment.

Patients with renal impairment:
OraVerse has not been studied in patients with renal impairment. OraVerse should be used with caution in these patients.

Elderly patients:
OraVerse dose adjustment is not required in elderly patients.

Administration

OraVerse should be administered by intraoral submucosal injection following the dental procedure using the same location(s) and technique(s) (infiltration or block injection) employed for the administration of the local anaesthetic.

OVERDOSAGE

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 contraction, visual disturbances, nausea, vomiting, diarrhea, or hypoglycemia.

For management of a suspected drug overdose, contact your regional Poison Control Centre for the latest information.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Phentolamine is a competitive non-selective α_1 and α_2-adrenergic receptor blocker of relatively short duration. When applied to vascular smooth muscle, it produces an α-adrenergic block resulting in vasodilatation.

Pharmacodynamics

The mechanism by which OraVerse accelerates reversal of soft-tissue anaesthesia is not fully understood. Phentolamine is not an antidote to local anaesthetics.

Pharmacokinetics

Following OraVerse administration, phentolamine is 100% available from the submucosal injection site and peak plasma concentrations are achieved 10-20 minutes 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 hours.

Pediatric population:
Following OraVerse administration, the phentolamine Cmax was higher (approximately 3.5-fold) in children who weighed between 15 and 30 kg 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 0.2 mg (½ cartridge).

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

STORAGE AND STABILITY

Store at controlled room temperature (15-25°C). Protect from direct heat and light. Do not refrigerate or freeze.

SPECIAL HANDLING INSTRUCTIONS

No special requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

OraVerse is a sterile solution for injection.

Composition

Edetate Disodium,
Mannitol,
Sodium Acetate,
Water for Injection
Acetic Acid or Sodium Hydroxide, for pH adjustment

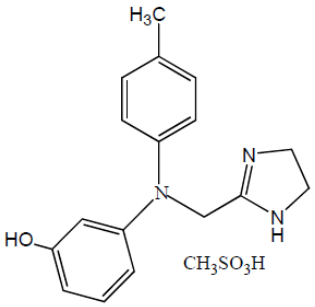
Packaging

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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name	Phentolamine Mesylate
Chemical Name	m-[N-(2-Imidazolin-2-ylmethyl)-p-toluidino] phenol monomethanesulfonate (salt) Phenol, 3-[[(4,5-dihydro-1H-imidazol-2-yl) methyl] (4-methyl-phenyl)amino]-, methanesulfonate (salt)
Structure Formula	
Molecular Formula	$C_{17}H_{19}N_3O \cdot CH_4O_3S$
Molecular Weight	377.46
Physicochemical Properties	Appearance: White or almost white, crystalline powder, which is slightly hygroscopic Melting Point: 178 - 182°C Solubility: soluble in water and in alcohol, slightly soluble in chloroform and practically insoluble in methylene chloride

CLINICAL TRIALS

Study Demographics and Trial Design

Table 2. Summary of patient demographics for the pivotal clinical trials

Study#	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)
Study 1 (NOVA 04-100)	Blinded, randomized, controlled	0 (sham), 0.4,0.8 mg Submucosal Single dose	244 (122 drug, 122 sham)	52 years (12-92 years)
Study 2 (NOVA 04-200)	Blinded, randomized, controlled	0 (sham), 0.4,0.8 mg Submucosal Single dose	240 (120 drug, 120 sham)	46 years (12-81 years)
Study 3 (NOVA 05-PEDS)	Blinded, randomized, controlled	0 (sham), 0.2,0.4 mg Submucosal Single dose	152 (96 drug, 56 sham)	8 years (4-11 years)

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 three clinical studies (Table 2). OraVerse-induced reversal of local anesthetic effects on the teeth, mandible and maxilla has not been assessed. The potential benefit of OraVerse concerning the reduction of self-inflicted injuries has not been studied in clinical trials.

Study 1 enrolled 76% of patients 18 to 64 years of age, and Study 2 had 78% that were 18 to 64 years of age. The remaining patients were almost equally distributed between the categories of 12 to 17 years (10-14%) and ≥65 years (11-12%). Fifty-two percent of the population was female.

In the pediatric Study 3, the treatment groups were balanced for ethnicity, age, grade, height, and weight. Nearly equal numbers of males and females were enrolled. The mean age was approximately 8 years.

Study Results

Two Phase 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 (i.e. teeth cleaning, scaling and planing, cavity filling, crowns) 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 for both studies. The secondary endpoints included time to patients' perception of recovered oral motor and sensory functions. In the mandibular study, the time to recovery of tongue sensation was also a secondary endpoint. OraVerse was administered within the hour of administration of local anesthetic in patients experiencing numbness in the lip. The dose of OraVerse was based on a cartridge ratio of 1:1 to local anesthetic. The control was a sham injection.

The median time to recovery of normal sensation in the lower lip was 70 minutes (95% confidence interval: 65 to 80 min) in the OraVerse group and 155 minutes (95% confidence interval: 140 to 165 min) in the sham control group. The median time to recovery of normal sensation in the upper lip was 50 minutes (95% confidence interval: 45 to 60 min) in the OraVerse group and 132.5 minutes (95% confidence interval: 115 to 145 min) in the control group. The differences between treatment groups in both studies were significant ($p < 0.0001$). The results for time to perceived return to normal oral motor and sensory functions were supportive of that of the primary endpoint.

A pediatric, Phase 2, double-blinded, randomized, multi-center, controlled study was conducted in dental patients who had received 2% lidocaine with 1:100,000 epinephrine (Study 3). Dental patients (n = 152, ages 4-11 years) received 1/2 cartridge of local anesthetic if they weighed 15 kg to 30 kg, and one-half or one full cartridge if they weighed more than 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 procedures, for mandibular and maxillary procedures combined, was 60 minutes (95% confidence interval: 45 to 75 minutes) in the OraVerse group and 135 minutes (95% confidence interval: 105 to 165 minutes) in the sham control group. The difference between treatment groups was statistically significant ($p < 0.0001$).

DETAILED PHARMACOLOGY

In a study on local blood flow in gingival/submucosal tissue of beagle dogs, phentolamine mesylate (0.012mg/kg) increased local blood flow when given after an intraoral injection of lidocaine HCl 2% with 1:100,000 epinephrine. The concentrations of phentolamine and lidocaine/epinephrine in the solutions administered in this study were comparable (based on body surface area) to the concentrations of these drugs used in clinical trials of OraVerse.

In an in vitro study conducted to assess the binding affinity to 58 types of human receptors, phentolamine at 377 ng/mL had strong and equal binding affinities at α1- and α2-adrenergic receptors, but had no appreciable binding at the other receptors tested.

TOXICOLOGY

Carcinogenesis and Mutagenesis

Carcinogenicity studies with OraVerse have not been conducted. In a study in rats dosed by oral gavage with 10, 50, and 150 mg/kg/day phentolamine mesylate for up to 101 weeks, hibernomas occurred in 3% of rats. The occurrence of hibernomas was not dose related and thought to be due to chronic adaptive responses secondary to the pharmacodynamic effects of the treatment.

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-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 the in vivo mouse micronucleus assay.

Reproductive toxicity and fertility impairment

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 sternebrae. 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.

At doses up to 150 mg/kg (143 times human therapeutic exposure levels at the Cmax), phentolamine mesylate was shown to have no adverse effects on male fertility in the rat.

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PART III: CONSUMER INFORMATION

[Pr]OraVerse
(Phentolamine Mesylate Injection House Standard)

This leaflet is part III of a three-part "Product Monograph: published when OraVerse was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OraVerse. Contact your dentist, doctor, nurse or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
OraVerse is used in adults and children, 6 years of age and older, to reverse the numbness in the lip caused by the injection of local anesthetic containing a vasoconstrictor. OraVerse is given by your dentist after a routine dental procedure (such as teeth cleaning, scaling and planing, cavity filling, and crowns).

What it does:
OraVerse increases blood flow in the blood vessels at the injection site. The return of normal sensation in the lip is accelerated after OraVerse injection.

When it should not be used:
OraVerse should not be used if you:

- are allergic (hypersensitive) to phentolamine mesylate or to any non-medicinal ingredientin the formulation.

What the medicinal ingredient is:
Phentolamine Mesylate

What the non-medicinal ingredients are:
edetate disodium, mannitol, sodium acetate, water for injection (acetic acid or sodium hydroxide).

What dosage forms it comes in:
Solution for Injection: 0.4 mg/1.7 mL

WARNINGS AND PRECAUTIONS

BEFORE you use OraVerse talk to your dentist, doctor, nurse, or pharmacist if you:

- have history of heart disease;
- are at increased risk for bleeding or are taking blood thinning medications;
- are pregnant; OraVerse is not recommended for use during pregnancy;
- are breastfeeding; It is not known whether OraVerse passes into breast milk.

OraVerse is not recommended for use in children less than 6 years of age or weighing less than 15 kg (33 lbs).
You should not eat or drink until normal oral sensation returns.
OraVerse will speed up the return of normal lip sensation, but can increase the feeling of pain in the mouth.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your dentist, doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with OraVerse:

- Drugs used to lower blood pressure.
- Drugs used to thin the blood (anti-coagulant medications)
- Antipsychotic drugs.

PROPER USE OF THIS MEDICATION

OraVerse is to be administered by injection into the mouth by a dentist.

OraVerse will be given to you at the end of the dental procedure, when the numbing effect of the local anesthetic is no longer needed.

OraVerse is injected in the mouth at the same location(s) and using the same technique(s) used for the injection of the local anesthetic.

You should not eat or drink until normal oral sensation returns.

Usual dose (adults and children 6 years and older):

- The dentist decides the dose based on your age and weight, as well as on the dose of local anesthetic used.
- The maximum dose is 2 cartridges for patients 18 years and older and 1/2 cartridge for patients aged 6-11 years.

If you think you have been given too much OraVerse which can lead to low blood pressure (dizziness, fainting) contact your dentist, doctor, nurse, pharmacist, hospital emergency department or regional Poison control Centre immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- pain at the site of the injection
- pain in the area of the dental procedure
- pain and/or tenderness in the mouth and jaw
- headache
- itching, tingling, prickling and burning
- stomach pain, diarrhea, vomiting

If any of these affects you seriously, tell your dentist, doctor, nurse or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your dentist, doctor, nurse, or pharmacist		Seek immediate medical help
		Only if severe	In all cases	
Uncommon	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
	Fast, slow or irregular heart beat	√		
	High Blood Pressure: headache, vision disorders, nausea and vomiting		√	
	Low Blood Pressure: dizziness, fainting, lightheadedness. May occur when you go from lying or sitting to standing up	√		
	Swelling of the face		√	

This is not a complete list of side effects. For any unexpected effects while taking OraVerse, contact your dentist, or doctor, nurse or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by of the following 3 ways:

Report Online at
www.healthcanada.gc.ca/medeffect
Call toll free telephone: 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  OTTAWA ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedeffectTM Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Septodont, Inc.
at 1-800-647-0643

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