# CONFIDENTIAL

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| **PROTOCOL NUMBER:** | **PHE-11-001** |
| **PROTOCOL TITLE:** | A Phase 4, Multicenter, Randomized, Double-Blinded, Controlled Study of OraVerse® for Safety and Efficacy in Pediatric Dental Patients Undergoing Mandibular and Maxillary Procedures |
| **STUDY DRUG:** | OraVerse (phentolamine mesylate) Injection |
| **DOSAGE FORM:** | Injectable Solution |
| **IND NUMBER:** | 65,095 |
| **SPONSOR:** | Novocol Pharmaceutical of Canada, Inc.<br>25 Wolseley Court<br>Cambridge, ON N1R 6X3 Canada<br>Tel: 519-623-4800<br>Fax: 519-623-4290 |
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| **STATISTICAL ANALYSIS:** | Tegra Analytics LLC<br>4445 Devine Street<br>Columbia, SC 29205<br>Tel: 803-217-0407<br>Email: matt@TegraAnalytics.com |
| **VERSION DATE:** | Version 4.0 September 2, 2011 |

## CONFIDENTIALITY STATEMENT

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## PROTOCOL SIGNATURE SHEET

The undersigned have reviewed the format and content of this protocol and have approved Protocol No. PHE-11-001 for issuance.

2011.09.06

Eric Penrose
Vice President of Quality Assurance North America
Novocol Pharmaceutical of Canada, Inc.

Date

20110906

Anita Hui
Director, Scientific and Regulatory Affairs
Novocol Pharmaceutical of Canada, Inc.

Date

**INVESTIGATOR SIGNATURE SHEET**

I have read the attached protocol and agree that it contains all the necessary details for performing the study.

I will provide copies of the protocol and the Investigator's Brochure on the study drug, which was furnished to me by the Sponsor, to members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the study drug and the conduct of the study.

Once the protocol has been approved by the Institutional Review Board (IRB), I will not modify this protocol without obtaining the prior approval of the Sponsor and of the IRB. I will submit the protocol modifications and/or any informed consent/assent form modifications to the Sponsor and the IRB, and approval will be obtained before any modifications are implemented.

I understand the protocol and will work according to it, the Code of Federal Regulations, the principles of Good Clinical Practice (current ICH guidelines), and the Declaration of Helsinki (1964) including all amendments.

_____

Investigator's Name (Print)

_____ _____

Investigator's Signature Date

**PROTOCOL SYNOPSIS for PHE-11-001**

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| **Protocol Number:** | PHE-11-001 |
| **Protocol Title:** | A Phase 4, Multicenter, Randomized, Double-Blinded, Controlled Study of OraVerse® for Safety and Efficacy in Pediatric Dental Patients Undergoing Mandibular and Maxillary Procedures |
| **Investigational Sites:** | Approximately 5-10 investigational sites |
| **Study Design:** | Multicenter, randomized, double-blinded, controlled study in pediatric dental patients 2 to 5 years of age. Eligible subjects will be randomized to OraVerse or sham injection.<br><br>There are 6 periods in the study: 1) screening, 2) anesthetic administration and dental procedure, 3) study drug administration, 4) observation period, 5) telephone follow-up, and 6) in-clinic safety follow-up.<br><br>All subjects 2-5 years of age will be assessed for safety. Subjects 4 and 5 years of age who are trainable in Wong-Baker FACES Pain Rating Scale (W-B PRS) will also be assessed for pain. Subjects 4 and 5 years of age who are trainable in the pediatric Functional Assessment Battery (pFAB) and lip and tongue palpation procedures will be assessed for efficacy. The observation period for all safety and efficacy assessments will be 2 hours.<br><br>A safety review of blinded data will be performed by the Medical Monitor for the study after 30 subjects have completed the study. |
| **Objectives:** | **Primary Objective**<br>Subjects 2-5 years of age<br>• to evaluate the safety and tolerability of OraVerse as measured by:<br>o incidence and severity of adverse events<br>o clinically significant changes in vital signs<br>o clinically significant changes in oral cavity assessments<br>o nerve injury<br>o analgesics required for intraoral pain<br>**Secondary Objectives**<br>Subjects 4 and 5 years of age who are trainable<br>o to evaluate the safety and tolerability of OraVerse as measured by incidence, severity and duration of intraoral pain and assessed by W-B PRS<br>o to determine if OraVerse accelerates the time to normal function as |

<table>
<tr><td></td><td>measured by a pediatric Functional Assessment Battery (pFAB)<br>o to determine if OraVerse accelerates the time to normal lip sensation as measured by standardized lip/tongue palpation procedure<br>o for mandibular procedures, to determine if OraVerse accelerates the time to normal tongue sensation as measured by standardized palpation procedure</td></tr>
<tr><td>Subject Population:</td><td>Approximately 150 subjects 2 to 5 years of age undergoing dental procedures requiring local anesthesia with lidocaine 2% with 1:100,000 epinephrine. The study will enroll 15 subjects each in the 2 and 3 year age group and 60 subjects each in the 4 and 5 year age group.</td></tr>
<tr><td>Duration of Study:</td><td>Approximately 12 months</td></tr>
<tr><td>Treatment Groups / Randomization:</td><td>Subjects will be randomized to OraVerse or sham in a 2:1 ratio. Randomization will be stratified by location of procedure (mandible or maxilla) and number of local anesthetic cartridges used (¼ cartridge, ½ cartridge or 1 cartridge). A balanced ratio of maxillary and mandibular procedures per site and the study overall randomization process will be ensured through Interactive Voice Response System (IVRS).</td></tr>
<tr><td>Blinding:</td><td>A visual barrier will be applied prior to study drug preparation and administration. The Investigator who administered the local anesthetic must administer the study drug. This Investigator is unblinded to study drug and will not perform subsequent assessments during the observation period. A blinded observer will be responsible for making safety and efficacy assessments. The Principal Investigator at the site has responsibility to maintain optimal study conduct and supervision of the protocol.</td></tr>
<tr><td>Treatment, Dose, Route:</td><td>Local anesthetic: lidocaine 2% with 1:100,000 epinephrine (¼ cartridge, ½ cartridge, or 1 full cartridge, depending on weight), administered by submucosal injection.<br><br>OraVerse: administered by submucosal injection at the same site as the local anesthetic. OraVerse is administered at the completion of the dental procedure using the same technique used for the local anesthetic.<br><br>OraVerse is administered on a 1-on-1 cartridge ratio to lidocaine. The dose of OraVerse and lidocaine will depend on the weight of the subject.
<table>
<tr><th>Subject's Weight (measured in kg)</th><th>Lidocaine/epinephrine Cartridge Amount</th><th>OraVerse Cartridge Amount (mg phentolamine mesylate)</th></tr>
<tr><td>≥ 10 kg to < 15 kg</td><td>¼</td><td>¼ (0.1 mg)</td></tr>
<tr><td>≥ 15 kg to < 30 kg</td><td>½</td><td>½ (0.2 mg)</td></tr>
<tr><td>≥ 30 kg</td><td>½ or 1</td><td>½ or 1 (0.2 or 0.4 mg)</td></tr>
</table></td></tr>
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| | Supplemental injections of lidocaine 2% with 1:100,000 epinephrine may be used to increase anesthesia in the local area as long as they are not likely to result in soft tissue anesthesia and are less than a total of 0.6 mL local anesthetic.<br>Sham injection: will mimic the time, preparation and application using a comparable dental tool and technique and will not penetrate tissue. |
| **Inclusion Criteria:** | A subject must meet the following eligibility criteria:<br>• Male or female, 2 to 5 years of age<br>• Sufficiently healthy as determined by the Investigator to receive routine dental care<br>• Requires a restorative procedure (restoration/filling) in a single quadrant of the mouth<br>• Requires local anesthesia with lidocaine 2% with 1:100,000 epinephrine administered by submucosal injection<br>• For subjects undergoing mandibular procedures, require an inferior alveolar nerve block for the restorative procedure<br>• Dental procedure(s) completed within 60 minutes of injection of local anesthetic<br>• For subjects 4 and 5 years of age, can be trained in pFAB and standardized lip/tongue palpation procedure<br>• Subjects who are trainable in pFAB and standardized lip/tongue palpation procedure have either:<br>o normal pFAB at baseline prior to administration of local anesthetic and<br>o at least one abnormal function (smiling, speaking, drinking or drooling) at the completion of the dental procedure<br>OR<br>o normal lip sensation at baseline prior to administration of local anesthetic and<br>o numbness of the relevant lip quadrant at completion of the dental procedure<br>• Subjects give written or verbal assent, as capable and appropriate, and parent(s) or legal guardian(s) give written informed consent. |
| **Exclusion Criteria:** | A subject will be ineligible if he/she meets any of the following criteria:<br>• Weight less than 10 kg<br>• Weight less than 15 kg if 4 or 5 years of age<br>• History or presence of any condition that contraindicates routine dental care or use of local anesthetic<br>• Requires more than ¼ cartridge of local anesthetic if weight is ≥ 10 kg and |

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| | < 15 kg, more than ½ cartridge of local anesthetic if weight is ≥ 15 kg and < 30 kg, and more than 1 cartridge of local anesthetic if weight is ≥ 30 kg, excluding supplemental injections<br>• Allergy or intolerance to lidocaine, epinephrine, sulfites, phentolamine, nitrous oxide or topical benzocaine<br>• Has used any investigational drug and/or participated in any clinical study within 30 days of study drug administration<br>• Has participated in this study or any previous study of phentolamine mesylate for reversal of local soft tissue anesthesia (STA)<br>• Any use of commercial OraVerse within 30 days of study drug administration<br>• Use of opioid or opioid-like analgesics within 24 hours prior to administration of local anesthetic<br>• Requires the use of local anesthetic other than lidocaine 2% with 1:100,000 epinephrine to perform the scheduled dental procedure<br>• Requires the use of general anesthesia or sedatives except for nitrous oxide to perform the scheduled dental procedure<br>• Any condition which in the opinion of the Investigator increases the risk to the subject of participating in this study or decreases the likelihood of compliance with the protocol |
| **Study Procedures and Assessments:** | There are 6 Periods in the Study:<br>**PERIOD 1:** Screening (Days -14 to Day 1)<br>• Informed consent/assent<br>• Medical/dental history and concurrent illness<br>• Demographics (including height and weight)<br>• Training for subjects 4 and 5 years of age in W-B PRS, pFAB and lip/tongue palpation procedure<br>• Complete assessment(s) of function and sensation prior to local anesthetic for subjects 4 and 5 years of age who are trainable<br>• Concomitant Medications and Concurrent Illness<br><br>Training will be performed prior to the initial assessments. Subjects who cannot be adequately trained in pFAB and lip/tongue palpation procedures and are not able to perform the study procedures are not eligible for study participation. Subjects who cannot be trained in the completion of the W-B PRS are eligible for enrollment in the study and will not perform these assessments.<br><br>**PERIOD 2:** Anesthetic Administration and Dental Procedure (Day 1)<br>• Vital signs: blood pressure and pulse<br>• General Oral Cavity Assessment |

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| | • If used, nitrous oxide and/or topical anesthetic<br>• Administration of lidocaine 2% with 1:100,000 epinephrine (¼, ½ or 1 cartridge, depending on weight)<br>• W-B PRS<br>• Specific Oral Cavity Assessment<br>• Dental procedure in one quadrant of mouth completed within 60 minutes of local anesthetic administration<br>• Concomitant Medications<br>• Concurrent Illness update, if any<br><br>**PERIOD 3:** Study Drug Administration (Day 1)<br>• Randomize to OraVerse or sham injection<br>• Assign unique subject identification number<br>• Administer study drug (OraVerse or sham) with visual barrier<br>• If nitrous oxide was used, wash-out for 5 minutes<br>• W-B PRS<br>• pFAB<br>• Sensation rating by lip/tongue palpation procedure<br>• General Oral Cavity Assessment<br>• Vital signs: blood pressure and pulse<br>• Concomitant Medications<br>• Adverse Events<br><br>**PERIOD 4:** Observation Period (Day 1)<br>The observation period for all subjects will be 2 hours. Subjects 2 to 5 years of age will be assessed for safety. W-B PRS assessments, pFAB, and lip/ tongue palpation procedures will be performed in subjects 4 and 5 years of age at defined intervals during the observation period.<br>• W-B PRS<br>• Vital Signs: blood pressure and pulse<br>• pFAB<br>• Sensation rating by lip/tongue palpation procedure<br>• General/Specific Oral Cavity Assessments<br>• Adverse Events<br>• Concomitant Medications<br>• Telephone and In-Clinic Follow-ups scheduled<br>• Discharge Time |

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| | **PERIOD 5:** Telephone Follow-up (Day 1)<br>Telephone Follow Up for adverse events including nerve injury and pain and concomitant medications. In-clinic Safety Follow-up scheduled<br><br>**PERIOD 6:** In-clinic Safety Follow-up (Days 2 or 3)<br>Adverse events including nerve injury, accidental injury and pain, concomitant medications and general/specific oral cavity assessments by a treatment-blinded investigator |
| **Statistical Methods:** | The safety and tolerability of OraVerse in this study will be assessed based on all subjects who are randomized and administered OraVerse or a sham injection. The exception will be the Wong-Baker FACES Pain Rating Scale which will be only assessed in subjects 4 and 5 years of age.<br><br>All safety-related interventions, events, and findings will be summarized by treatment group (OraVerse, sham), location of procedure (mandible, maxilla), age groups (2, 3, 4, 5 years), number of local anesthetic used (¼, ½, or 1 cartridge), and pooled across all subjects.<br><br>The incidence and duration of treatment emergent adverse events will be summarized according to the reporting conventions described above. An adverse event will be considered treatment emergent if the onset date and time occur on or after the recorded clock time of the injection of OraVerse or the sham injection. Adverse events will be coded to preferred terms and system organ classes according to the Medical Dictionary for Regulatory Activities (MedDRA®). The severity of each adverse event will be determined from the World Health Organization (WHO) Toxicity Criteria or by protocol specified criteria.<br><br>The incidence of abnormalities of the oral cavity, procedure site and injection sites will be reported by timepoint based on the findings from the serial assessments. The incidence of clinically significant changes (if any) will be tabulated along with the associated adverse event(s).<br><br>Vital sign results (blood pressure and pulse) will be summarized at each of the protocol specified assessments by calculating the mean, standard deviation, median, and range. In addition, the number and proportion of subjects in each treatment group who have an increase or decrease from baseline that exceed predefined threshold values will be reported.<br><br>Nerve injuries, if any, will be tabulated by treatment group.<br><br>For subjects 4 and 5 years of age the incidence, severity, and duration of intraoral pain will be evaluated using the Wong-Baker FACES pain rating scale. Pain of injection and pain at the procedure site will be assessed separately. Analgesic requirements will be summarized by the number and proportion of subjects who take at least one analgesic medication for the treatment of intraoral pain following the administration of OraVerse or the sham injection. The administration of concomitant medications, including analgesics, will be tabulated by medication class and by drug dictionary term |

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| | within medication class according to the WHO Drug dictionary.<br><br>The efficacy of OraVerse will be evaluated for subjects 4 and 5 years of age, who are trainable in pediatric FAB (pFAB) and standardized lip/tongue palpation procedures, and who meet final eligibility criteria related to abnormal pFAB and/or lip numbness at the completion of the dental procedure. The determination of evaluability for efficacy will be made prior to randomization to OraVerse or the control treatment. Separate evaluability determinations will be made for the pFAB and lip/tongue sensation tests.<br><br>The time to normal function (pFAB) will be summarized descriptively by treatment group using the Kaplan-Meier method. The estimated median for each treatment group and corresponding 95% confidence interval will be reported. The stratified log-rank test will be used to test the null hypothesis that the distributions for the time to recovery of normal sensation of the lip are equal between the two treatment groups versus the alternative hypothesis that distributions are different. The strata formed by the location of procedure (mandible or maxilla) stratification factors will be used for computing the stratified log-rank test statistic.<br><br>The above methods also will be used for the other time to event endpoints based on the time to recovery of normal sensation of the lip and tongue. |

**ABBREVIATIONS**

| | |
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| AE | adverse event |
| CFR | Code of Federal Regulations |
| CRF | Case Report Form |
| ECG | electrocardiogram |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICH | International Conference on Harmonisation |
| IRB | Institutional Review Board |
| IV | intravenous |
| IVRS | Interactive Voice Response System |
| MedDRA® | Medical Dictionary for Regulatory Activities |
| NF | National Formulary |
| OraVerse® | Investigational agent |
| OCA | Oral Cavity Assessment |
| PHI | Personal Health Information |
| SAE | serious adverse event |
| Sponsor | Novocol Pharmaceutical of Canada, Inc.; Novocol |
| STA | soft tissue anesthesia |
| Study Drug | OraVerse or sham administration |
| USP | United States Pharmacopoeia |
| WHO | World Health Organization |
| WMA | World Medical Association |
| W-B PRS | Wong-Baker FACES Pain Rating Scale |

## 1. INTRODUCTION

OraVerse has been approved by FDA for the reversal of soft tissue anesthesia, 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 in dental patients 6 years of age and older and weighing 15 kg (33 lbs) or more. OraVerse was studied for efficacy in children 4 and 5 years of age however the product is not currently approved for use in the study population of children 2 to 5 years of age.

As part of the clinical development program for OraVerse, two Phase 3 studies (Studies NOVA 04-100 and NOVA 04-100) were conducted with a total of 484 adolescent and adult dental patients (Hersh E.V. et al, 2008). A pediatric Phase 2 study (Study NOVA 05-PEDS) enrolled 152 dental patients aged 4 to 11 years of age (Tavares M. et al, 2008). The pharmacokinetic profile of OraVerse and its effect on lidocaine 2% was evaluated in two clinical studies, one enrolling adult dental patients (Moore P.A. et al., 2008), the second enrolling pediatric dental patients 3 to 17 years of age (Study NOVA 04-PK and NOVA 05-PEDS-PK, respectively).

Pediatric dental patients may be more likely to accidental injury than adults and will likely benefit from accelerated local anesthesia reversal. One study enrolling 320 patients 2 to 18 years of age found that 13% of all patients experienced post-operative soft tissue trauma. By age group, trauma frequency was 18% for subjects less than 4 years of age, 16% for subjects 4 to 7 years of age, 13% for subjects 8 to 1 years of age and 7% for subjects aged 12 to 18 years (College C. et al., 2000). A more recent study in 264 dental patients 2 to 14 years of age receiving articaine for restorative procedures reported that soft tissue injury occurred in 14% of subjects at 3 hours and was found to be highest among children less than 7 years of age (Adewumi A. et al., 2008).

This Phase 4 clinical study is designed as a multicenter, randomized, double-blinded, controlled study to evaluate the safety and efficacy of OraVerse in approximately 150 children 2 to 5 years of age. OraVerse or sham injection is administered at the completion of a dental procedure requiring local anesthesia with lidocaine 2% with 1:100,000 epinephrine. The dental procedure(s) comprising restoration/fillings shall be performed in a single quadrant of the mouth.

The primary endpoint is safety and tolerability of OraVerse as measured by adverse events, vital signs, oral cavity assessments, nerve injury, and analgesics for intraoral pain. Secondary objectives in subjects 4 and 5 years of age include the safety and tolerability of OraVerse as measured by pain assessments using W-B PRS and evaluation of efficacy assessed by a pediatric Functional Assessment Battery (pFAB) and standardized lip and tongue palpation procedure.

The study is summarized in a flow chart (Appendix A) and in a schedule of time and events (Appendix B).

## 1.2 Rationale for Selection of Dose

In this Phase 4 study, three doses of OraVerse will be evaluated: 0.1 mg, 0.2 mg and 0.4 mg phentolamine mesylate. The dose will depend upon the weight of the subject and the volume of local anesthetic administered (quarter, half or whole cartridge). The doses of OraVerse administered in this study are summarized in Table 1:

**Table 1: Local Anesthetic and OraVerse Dose**

| Subject's Weight (measured in kg) | Lidocaine/epinephrine Cartridge Amount | OraVerse Cartridge Amount (mg of phentolamine mesylate) |
|---|---|---|
| ≥ 10 kg to < 15 kg | ¼ | ¼ (0.1 mg) |
| ≥ 15 kg to < 30 kg | ½ | ½ (0.2 mg) |
| ≥ 30 kg | ½ or 1 | ½ or 1 (0.2 or 0.4 mg) |

Study drug will be administered at the same site as local anesthetic at the completion of the dental procedure. Subjects randomized to OraVerse who receive ¼, ½ or 1 cartridge of local anesthetic will receive ¼, ½ or whole cartridge of OraVerse, respectively, to maintain a 1:1 ratio. Subjects randomized to control will receive a sham injection that mimics the injection of local anesthetic without penetration of tissues.

The mg/kg dose of phentolamine administered in the pediatric Phase 2 study NOVA 05-PEDS and the approved labeling of OraVerse were considered in the selection of doses for the current study. In study NOVA 05-PEDS, pediatric subjects 4 to 11 years of age received ½ cartridge of local anesthetic and OraVerse if weighing 15 to < 30 kg and either ½ cartridge or a full cartridge if weighing ≥ 30 kg. The prescribing information for OraVerse recommends a maximum of ½ cartridge (0.2 mg) of OraVerse for pediatric subjects weighing between 15 and ≤ 30 kg. OraVerse is currently not recommended for use in children less than 6 years of age or weighing less than 15 kg (33 lbs).

The study population in this Phase 4 study consists of pediatric dental patients 2 to 5 years of age. It is expected that some patients 2 or 3 years of age will weigh less than 15 kg. In order not to exceed the maximum dose administered to pediatric dental patients during the study, subjects weighing between 10 and < 15 kg will receive ¼ cartridge of OraVerse and subjects less than 10 kg will be excluded from the study. Subjects weighing between 15 and ≤ 30 kg and subjects weighing ≥ 30 kg will receive the doses administered in the pediatric Phase 2 study NOVA 05-PEDS.

The dosing scheme according to subject's weight is summarized in Table 2:

**Table 2: Dosing scheme according to subject's body weight**

| Body Weight | | Dosing Scheme | | |
|---|---|---|---|---|
| Lbs | kg | Cartridge Amount | Phentolamine Dose (mg) | Phentolamine Dose (mg/kg) |
| 22 | 10 | ¼ | 0.1 | 0.010 |
| 33 | 15 | ½ | 0.2 | 0.013 |
| 44 | 20 | ½ | 0.2 | 0.010 |
| 55 | 25 | ½ | 0.2 | 0.008 |
| 66 | 30 | 1 | 0.4 | 0.013 |
| 88 | 40 | 1 | 0.4 | 0.010 |
| 110 | 50 | 1 | 0.4 | 0.008 |

As can be seen in the rightmost column in the table above, the doses in mg/kg for this study fall within the range administered in the pediatric Phase 2 study NOVA 05-PEDS and deemed safe.

### 1.3 Rationale for Selection of Control

A sham injection was selected as the control for this Phase 4 study to minimize bias of assessments of safety for OraVerse and the second injection. This type of control was effectively used in the Phase 3 studies NOVA 04-100 and NOVA 04-200 and the pediatric Phase 2 study NOVA 05-PEDS.

Precautions will be taken to maintain blinding in this study (see Section 6.3.2).

### 1.4 Assessment Instruments

#### 1.4.1 Wong-Baker FACES Pain Rating Scale

The Wong-Baker FACES Pain Rating Scale (WB-PRS) was selected as the instrument to assess pain (Wong D.L and Baker C.M., 2001) following injection of OraVerse or the sham injection in subjects 4 to 11 years of age in Study NOVA 05-PEDS. This scale will also be used for assessment of pain in subjects 4 to 5 years of age who are trainable in WB-PRS. Scores greater than 2 ("hurts a little more") will be considered clinically relevant pain. The W-B PRS is described in Appendix C.

The use of analgesics for intraoral pain following the dental procedure will also be evaluated in the assessment of pain.

#### 1.4.2 Pediatric Functional Assessment Battery

A functional assessment battery (FAB) was previously developed by Novalar Pharmaceuticals Inc. in collaboration with dental and oral function specialists to assess smiling, speaking,

drinking, and drooling in dental patients with soft tissue anesthesia in two Phase 3 studies (NOVA 04-100 and NOVA 04-200), which enrolled adolescent and adult dental patients ≥ 12 years of age. The FAB was used to evaluate time to normal function as a secondary efficacy endpoint in these studies. Appropriate age-specific modifications have been made to the FAB to allow the evaluation of functional deficits in 4 and 5 year old dental patients (pediatric functional assessment battery [pFAB]). Based on feedback from Novalar's pediatric clinical advisory board it would not be feasible to train dental patients 2 and 3 years of age reliably on the pFAB procedures, consequently, the pFAB will not be performed by these age groups.

In cooperation with a pediatric clinical advisory board and a speech-language pathologist, the FAB used in the Phase 3 studies was adapted to the age group tested in this clinical study, i.e. dental subjects 4 and 5 years of age. Drinking will be tested using a modified drinking test (DePippo, K.L. et al., 1992); the amount of water for drinking was reduced from 3 ounces of water to 1 ounce of a beverage of choice. Novalar developed the speaking test for the adult FAB used in the Phase 3 studies and modifications for the pFAB in cooperation with Dr. Jeri Logemann at Northwestern University. Speaking in the Phase 4 study will be tested by having the pediatric subject repeat 10 words that require articulation of sounds requiring normal motor/sensory function of the tongue (Fisher H.B. and Logemann J.A., 1971). Smiling is part of testing the motor component of the seventh cranial nerve in standard neurological examination. Drooling is tested by visual observation.

These four functions are required to be tested in the following sequence: 1) smiling, 2) speaking, 3) drinking, and 4) drooling. The outcome of the smiling, speaking, and drinking tests is to be rated "normal" or "abnormal" by the observer only. The test for drooling is to be rated by the observer as "absent" or "present" which will be interpreted as "normal" or "abnormal", respectively. The standardized instructions provided to subjects and observers are provided in Appendix D. The criteria used for each rating are provided in Table 3 below.

**Table 3: Functional Assessment Battery Rating Criteria**

| Function | Rating | Definition |
|---|---|---|
| Smiling, Speaking, Drinking | Normal | Normal for each function is defined as "same as" or "equivalent" to performance of test prior to dental procedure (baseline) |
| | Abnormal | Abnormal for each function is defined as "not normal", i.e., different from baseline. Examples are given under the instructions for rating each test. |
| Drooling | Present | Presence of drooling is to be interpreted as "abnormal" |
| | Absent | Absence of drooling is to be interpreted as "normal" |

Based on the result of the 4 individual functional tests, a subject is considered to have "normal function" if all of these tests are rated "normal" (for smiling, speaking, and drinking tests) or "absent" (for drooling test) by observer ratings. A subject is considered to have "abnormal function" if one or more of these tests are rated "abnormal" (for smiling, speaking, and drinking tests) or "present" (for drooling test) by observer ratings.

Dental experts indicated that there was no safety issue with testing smiling, speaking, drinking or drooling in dental patients with STA, as long as the fluids used in the drinking test were at room temperature. Eating was not included in the battery because of the potential for accidental injury (biting of lip, cheek or tongue) while STA persists.

### 1.4.3 Lip and Tongue Palpation for Soft Tissue Anesthesia

Palpation consists of soft tapping of the upper or lower lip with the subject's index or middle finger. Similarly, tongue palpation consists of tapping of the tongue at the side of the dental procedure for subjects undergoing mandibular dental procedures only. Subjects will rate the status of their soft-tissue anesthesia as either abnormal or normal. The blinded observer will use terms such as "feels different", "numb", "funny", "fuzzy", or "frozen" to elicit the information about their soft-tissue anesthesia status. Standardized instructions for lip and tongue palpation are presented in Appendix E.

### 1.4.4 General and Specific Oral Cavity Assessments

General and specific oral cavity assessments (OCA) will be performed to evaluate complications of submucosal injection(s). The general oral cavity assessment consists of a broad evaluation of the mouth. The specific oral cavity assessments consist of evaluations of oral tissues at the injection site(s) and procedure site(s). Clinically significant abnormalities for the OCAs will be recorded as adverse events on the appropriate CRF.

## 1.5 Potential Risks to Participants

Potential risks to subjects participating in this study are side effects due to administration of OraVerse, local anesthetics, and the dental procedure. A mild and transient increase in pain is the most likely risk associated with administration of OraVerse.

Potential risks to subjects participating in this study are minimized in this protocol by the following:

- Exclusion of subjects weighing less than 10 kg
- Limiting the dose of lidocaine 2% with 1:100,000 epinephrine by submucosal injection to one cartridge (excluding supplemental injections) in subjects ≥ 30 kg, ½ cartridge (excluding supplemental injections) in subjects weighing ≥ 15 kg to < 30 kg, and ¼ cartridge in subjects weighing ≥ 10 kg to < 15 kg
- Use of a sham administration as the control eliminates the risk associated with a second administration for those subjects randomized to the control group
- Limiting the dose of OraVerse by submucosal injection to 0.4 mg phentolamine mesylate in subjects weighing ≥ 30 kg, 0.2 mg phentolamine mesylate in subjects weighing ≥ 15 kg but < 30 kg, and 0.1 mg for subjects between ≥ 10 kg and < 15 kg
- Exclusion of subjects with allergies to or intolerance of topical benzocaine, lidocaine, epinephrine, sulfites, nitrous oxide or phentolamine
- Selection of qualified Investigators and training of study personnel

- Monitoring by trained study staff during the observation period
- Providing guidelines for management of toxicity

This study is being performed in compliance with the guidelines of the International Conference on Harmonisation (ICH), Good Clinical Practice (GCP).

### 1.6 Subject's Duration of Participation

The participation of a subject will be completed on Day 2 or 3, the day of the in-clinic safety follow-up visit, unless the subject experiences an adverse event, whereby subject will be followed-up until resolution of the adverse event or the condition has stabilized as outlined in Sections 7.1 and 7.6 or withdrawn earlier from the study as specified in Section 9.3.2. No provisions for additional care will be given to the subject once their participation in the study has ended, the subject will resume standard dental care.

## 2. STUDY OBJECTIVES

The primary objective of this study is to evaluate the safety and tolerability of OraVerse in subjects 2 to 5 years of age as measured by:

- incidence and severity of adverse events
- clinically significant changes in vital signs
- clinically significant changes in oral cavity assessments
- nerve injury
- analgesics required for intraoral pain

Secondary objectives in subjects 4 and 5 years of age who are trainable in pFAB and standardized lip/tongue palpation procedures include the following:

- to evaluate the safety and tolerability of OraVerse as measured by incidence, severity and duration of intraoral pain using the W-B PRS
- to determine if OraVerse accelerates the time to normal function as measured by a pFAB
- to determine if OraVerse accelerates the time to normal lip sensation as measured by standardized lip/tongue palpation procedure
- for mandibular procedures, to determine if OraVerse accelerates the time to normal tongue sensation as measured by standardized lip/tongue palpation procedure

## 3. STUDY DESIGN

This Phase 4 study is designed as a multicenter, randomized, double-blinded, controlled study to evaluate the safety and efficacy of OraVerse administered as a submucosal injection following completion of a restorative procedure requiring local anesthesia with lidocaine 2% with 1:100,000 epinephrine in dental patients 2 to 5 years of age. The study will enroll the following number of pediatric dental patients in different age groups (Table 4).

**Table 4: Subject Sample Distribution by Age Group**

| Age Group | Number of OraVerse Subjects | Number of Sham Subjects |
|---|---|---|
| 2 years | 10 | 5 |
| 3 years | 10 | 5 |
| 4 years | 40 | 20 |
| 5 years | 40 | 20 |
| Total | 100 | 50 |
| **Total Study: 150 Subjects** | | |

After obtaining assent/informed consent from the subject/parent or legal guardian, pediatric dental patients scheduled to undergo a restorative procedure will be screened for eligibility, assigned a screening number, undergo baseline assessments and training, and then receive local anesthesia.

After the dental procedure, subjects who have at least one abnormal pFAB test and/or numbness of the lip will be randomized to OraVerse or control (sham injection) in a 2:1 allocation ratio, respectively, and stratified according to location of the dental procedure (mandible or maxilla) and amount of local anesthetic (¼, ½ or 1 cartridge).

Study drug will be administered at the same site as the local anesthetic using the same injection technique. The Investigator who administers local anesthetic and study drug may be the same or different from the dentist who completes the dental procedure. Precautions will be taken to maintain the blind.

All subjects will be assessed for safety. Subjects 4 and 5 years of age who are trainable in Wong-Baker FACES Pain Rating Scale (W-B PRS) will also be assessed for pain. Subjects 4 and 5 years of age who are trainable in pediatric Functional Assessment Battery (pFAB) and lip and tongue palpation procedures will be assessed for efficacy. The observation period for all safety and efficacy assessments will be 2 hours. During this observation period, study procedures will be performed by study staff who are blinded to the treatment assignment.

The subject's parents/legal guardian will be contacted by telephone on the same day (Day 1) to evaluate adverse events, analgesics required for intraoral pain, and other concomitant medications. All subjects will visit the dental clinic on Days 2 or 3 for an in-clinic safety follow-up of adverse events including nerve injury, accidental injury, and pain, concomitant medications and a general/specific oral cavity assessment by a treatment-blinded investigator.

As a primary objective, the study will evaluate the safety and tolerability of OraVerse as measured by the incidence and severity of adverse events, incidence, severity and duration of intraoral pain as measured by the W-B PRS, clinically significant changes in vital signs and oral cavity assessments, nerve injury and analgesics required for intraoral pain.

As secondary objectives for subjects 4 and 5 years of age who are trainable in pFAB and standardized lip/tongue palpation procedures, the study will assess pain using W-B PRS and determine if OraVerse accelerates the time to normal function and lip sensation as measured by standardized lip/tongue palpation procedures. In addition, the study will determine if OraVerse accelerates the time to normal tongue sensation in mandibular procedures as measured by standardized lip/tongue palpation procedure.

The study will be completed when subject distribution in Table 4 has been met and a minimum of 150 subjects have been randomized to study drug and have completed the procedures of the protocol.

### 3.1 Study Periods

There are 6 periods in the study:

Period 1: Screening (Days -14 to Day 1)
Period 2: Anesthetic Administration and Dental Procedure (Day 1)
Period 3: Study Drug Administration (Day 1)
Period 4: Observation (Day 1)
Period 5: Telephone Follow-Up (Day 1)
Period 6: In-clinic Safety Follow-up (Day 2 or 3)

Study procedures and assessments for safety and efficacy in these periods are outlined in Section 6. A flow chart of the study and schedule of assessments are provided in Appendices A and B, respectively.

### 3.2 Safety Review

A safety review using blinded data will be performed by the Medical Monitor after 30 subjects have completed the study to ensure the subjects are not exposed to undue risk. The safety and tolerability of OraVerse will be evaluated based on the following parameters:

- incidence and severity of adverse events
- clinically significant changes in vital signs (blood pressure and pulse)
- clinically significant changes in oral cavity assessments
- nerve injury
- analgesics required for intraoral pain

### 3.3 Blinding

The following measures will be taken to maintain the blind:

- a visual barrier will be placed that obstructs the subject's view of the preparation and administration of study drug.
- administration of study drug will be performed by the same Investigator who injected local anesthetic. This Investigator is unblinded to study drug and will not perform subsequent assessments during the observation period. A blinded observer will be responsible for making safety and efficacy assessments. The Principal Investigator will maintain optimal study conduct and supervision of the protocol although they may not be directly involved with the subject.
- the Investigator performing the injection will return study drug cartridges to the study kit and seal the kit closed using tamper-evident labels prior to removing visual barrier from the subject and study personnel involved in subsequent assessments returning to the procedure room.
- study personnel who are involved in assessments following the preparation and administration of study drug will not be present in the room at the time of the preparation and administration of study drug but will be informed about the site(s) of administration and the site of the procedure.
- adverse events will be monitored and recorded by blinded study personnel.

In the event of a medical emergency requiring unblinding to determine the appropriate medical treatment, the contents of the kit can be determined by scratching off the overlay of kit label. In the event that unblinding is required, the Investigator will notify the Sponsor and the Sponsor's Medical Monitor within 24 hours. Should any opening of a sealed study kit occur, this must be recorded in the source documents and Case Report Form (CRF). Any other breaking of the blind with exception of a medical emergency will be considered a protocol violation.

### 3.4 Randomization

Upon completion of the dental procedure and confirmation that all study eligibility criteria are met, eligible subjects will be randomized to receive OraVerse or control (sham injection) in a 2:1 allocation ratio, respectively. Randomization will be performed by authorized study staff using an Interactive Voice Response System (IVRS). The randomization will be stratified by location of the dental procedure (mandible or maxilla) and number of local anesthetic cartridges used (¼, ½ or 1). Randomization confirmation will be retained in the study site's source documents. A ratio of maxillary and mandibular procedures per study site and across the study will be ensured through IVRS.

Randomized subjects will be assigned a unique subject identification number. This number will be used to formally identify all study subjects and will be the identification number recorded on all case report forms.

## 4. SELECTION CRITERIA

Approximately 150 subjects will be randomized to study drug (OraVerse or sham). Potential subjects will be recruited at investigational sites or from parents/legal guardians responding to IRB-approved advertisements, posters or brochures.

### 4.1 Inclusion Criteria

A subject must meet the following eligibility criteria:

- Male or female, 2 to 5 years of age
- Sufficiently healthy as determined by the Investigator to receive routine dental care
- Requires a restorative procedure (restoration/filling) in a single quadrant of the mouth
- Requires local anesthesia with lidocaine 2% with 1:100,000 epinephrine administered by submucosal injection
- For subjects undergoing mandibular procedures, require an inferior alveolar nerve block for the restorative procedure
- Dental procedure(s) completed within 60 minutes of injection of local anesthetic
- For subjects 4 and 5 years of age, can be trained in standardized lip/tongue palpation procedure and pFAB
- Subjects who are trainable in pFAB and standardized lip/tongue palpation procedure have either:
    - normal pFAB at baseline prior to administration of local anesthetic and
    - at least one abnormal function (smiling, speaking, drinking or drooling) at the completion of the dental procedure

  OR
    - normal lip sensation at baseline prior to administration of local anesthetic and
    - numbness of the relevant lip quadrant at completion of the dental procedure
- Subjects give written or verbal assent, as capable and appropriate, and parent(s) or legal guardian(s) give written informed consent

### 4.2 Exclusion Criteria

A subject will be ineligible if he/she meets any of the following criteria:

- Weight less than 10 kg
- Weight less than 15 kg if 4 or 5 years of age
- History or presence of any condition that contraindicates routine dental care or use of local anesthetic

- Requires more than ¼ cartridge of local anesthetic if weight is ≥ 10 kg and < 15 kg, more than ½ cartridge of local anesthetic if weight is ≥ 15 kg and < 30 kg, and more than 1 cartridge of local anesthetic if weight is ≥ 30 kg, excluding supplemental injections
- Allergy or intolerance to lidocaine, epinephrine, sulfites, phentolamine, nitrous oxide or topical benzocaine
- Has used any investigational drug and/or participated in any clinical study within 30 days of study drug administration
- Has participated in this study or any previous study of phentolamine mesylate for reversal of local soft tissue anesthesia (STA)
- Any use of commercial OraVerse™ within 30 days of study drug administration
- Use of opioid or opioid-like analgesics within 24 hours prior to administration of local anesthetic
- Requires the use of local anesthetic other than lidocaine 2% with 1:100,000 epinephrine to perform the scheduled dental procedure
- Requires the use of general anesthesia or sedatives except for nitrous oxide to perform the scheduled dental procedure
- Any condition which in the opinion of the Investigator increases the risk to the subject of participating in this study or decreases the likelihood of compliance with the protocol

## 4.3 Subject Withdrawal (Premature Discontinuation from the Study)

### 4.3.1 Subject Withdrawal Criteria

Subjects may withdraw from the study at any time without providing a reason. The investigator may also withdraw a subject due to an unacceptable AE. Under these circumstances, the investigator will institute the appropriate follow-up investigations in accordance with accepted standards of medical care, including performance of tests at the time of withdrawal.

### 4.3.2 Reporting Discontinuations

All premature subject discontinuations will be listed in the final clinical study report. Discontinuations for safety reasons will be promptly reported to regulatory authorities and the study Institutional Review Board (IRB), according to the procedures outlined in Section 7.

### 4.3.3 Replacement of Subjects

Subjects who decide to withdraw from the study or are withdrawn from the study by the PI for non-safety reasons will be termed "drop-outs". Subjects who are withdrawn by the investigator because of an unacceptable AE will be termed a "withdrawal". No subjects will be replaced.

# 5. STUDY TREATMENTS

## 5.1 OraVerse

OraVerse is manufactured by Novocol Pharmaceutical of Canada, Inc. (Cambridge, Canada) as a sterile, pyrogen free, isotonic solution for administration in glass dental cartridges that deliver 0.4 mg phentolamine mesylate in 1.7 mL (per cartridge). The concentration of the active ingredient (phentolamine mesylate) in OraVerse is 0.235 mg/mL.

- Phentolamine mesylate (*m*-[*N*-(2-imidazolin-2-ylmethyl)-*p*-toluidino]phenol mono methanesulfonate) is a white or off-white, odorless crystalline powder that is soluble in water and alcohol, and slightly soluble in chloroform. The molecular formula is $C_{17}H_{19}N_3O \cdot CH_4O_3S$, and the molecular weight is 377.47.

- Excipients include water for injection, ethylenediaminetetraacetic acid (EDTA), D-mannitol, sodium acetate, and acetic acid or sodium hydroxide for pH adjustment.

## 5.2 Packaging, Supply, and Labeling

Cartridges will contain OraVerse or will be empty; empty cartridges for sham administration will not be labeled. The cartridge label for OraVerse will be the approved product labeling for the US market.

Study drug is packaged in kits containing 2 cartridges (the extra cartridge is supplied in case of damage or malfunction). The kits are labeled with double-blind labels with a tear-off portion to affix to the appropriate case report form (CRF). The tear-off portion will contain a scratch-off area to unblind that particular kit in case of a medical emergency. An example of the kit label that includes the protocol number, contents, kit (randomization) number, subject number, and date dispensed, route of administration, storage conditions, caution statement "Investigational New Drug Limited by (US) Law to Investigational Use Only" and statement "Manufactured by: Novocol Pharmaceutical of Canada, Inc., Cambridge, ON, Canada N1G 5A1" is shown below (the tear-off portion is not shown). Study kits will be packaged and shipped in a tertiary box.

**Protocol No.: PHE-11-001**
**Contents: 2 Cartridges**
Each Cartridge for Single Use Only
Date Dispensed: _____
Subject Number: _____
Site # XX Kit # XXXXX
Administer by Intraoral Submucosal Injection
Store at Room Temperature (59-86°F)
**Caution:** Investigational New Drug Limited by (US) Law to Investigational Use Only
**Manufactured by**:
Novocol Pharmaceutical of Canada, Inc., Cambridge, ON, Canada N1G 5A1

### 5.3 Storage of OraVerse (Study Drug)

Cartridges of study drug will be stored under secured conditions with limited access at temperatures between 15° - 30°C (59° - 86°F). The cartridges should be kept in the study kits until the time of use. Direct exposure to heat and light should be avoided. Immediately following administration of study drug (OraVerse or sham), empty cartridges will be replaced in the kit and the kit will be sealed closed with tamper evident labels for future drug accountability by the Investigator performing the investigational procedure. Compliance with administration of study drug will be monitored through study drug accountability as recorded on source documents and CRFs (see Section 9.1.7).

### 5.4 Study Drug

At the completion of the dental procedure and assessments, study drug (OraVerse or sham) will be administered at the same site(s) that local anesthetic was administered using the same intraoral injection technique(s) (except for supplemental infiltrations). The sham injection will be performed without making an actual injection at the local anesthetic sites; however, will mimic the time, preparation and application using a comparable dental tool and technique. Compliance with administration of study drug will be monitored through study drug accountability as recorded on source documents and CRFs.

The highest dose of phentolamine to be administered in this Phase 4 study is 0.4 mg. Study NOVA 05-PEDS enrolled pediatric subjects 4-11 years of age who were treated with 0.4 or 0.2 mg of phentolamine mesylate, dependent on weight. This study will also use 0.1 mg phentolamine mesylate in subjects weighing between 10 and < 15 kg.

### 5.5 Topical and Local Anesthetics

Benzocaine (20%) topical gel will be obtained by the site through a commercial source and may be used to provide local anesthesia of mucosal surfaces within 30 seconds of application. It has a short duration (approximately 15 minutes) and has virtually no systemic absorption (see package insert of manufacturers).

Local anesthetics (lidocaine 2% with 1:100,000 epinephrine) will be supported by the Sponsor through a commercial source and used to provide local anesthesia for the scheduled dental procedure. The dose of lidocaine 2% with 1:100,000 epinephrine will depend upon the weight of the pediatric subject:

| Subject's Weight (measured in kg) | Lidocaine/epinephrine Cartridge Amount | OraVerse Cartridge Amount (mg of phentolamine mesylate) |
|---|---|---|
| ≥ 10 kg to < 15 kg | ¼ | ¼ (0.1 mg) |

| | | |
|---|---|---|
| ≥ 15 kg to < 30 kg | ½ | ½ (0.2 mg) |
| ≥ 30 kg | ½ or 1 | ½ or 1 (0.2 or 0.4 mg) |

Supplemental injections of lidocaine 2% with 1:100,000 epinephrine may be used to increase anesthesia in the local area as long as they are not likely to result in soft tissue anesthesia and are less than a total of 0.6 mL local anesthetic. As supplemental, these injections are not likely to result in STA of the lip and/or tongue, and study drug will not be administered in locations of these injections.

Care will be taken during the administration to avoid intravascular administration. The risks of submucosal administrations of lidocaine 2% with 1:100,000 epinephrine are detailed in the package inserts of the various manufacturers.

## 6.0 STUDY PROCEDURES

Study procedures and assessments for safety and efficacy are detailed in Appendix B. Subjects' screening and/or randomization information will be recorded on the Screening and Enrollment log.

### 6.1 PERIOD 1 - Screening (Day -14 to Day 1)

Subjects will be screened within 14 days of dosing with study drug and may be screened on the same day of their scheduled dental procedure (Day 1).

#### 6.1.1 Initial Screening (Day -14 to Day 1)

After obtaining written or verbal assent, as capable and appropriate, and informed consent from the parent or legal guardian for a potential subject, a unique screening number will be assigned and the following evaluations will be performed to screen for eligibility:

- Medical/dental history and concurrent illness
- Demographics (including height, weight and grade level)

#### 6.1.2 Subject Training (Day 1)

Subjects 4 and 5 years of age only will be trained to perform the following assessments:

- W-B PRS (see Appendix C)
- pFAB (see Appendix D)
- Sensation rating by lip/tongue palpation (tongue palpation for mandibular procedures) (see Appendix E)

Training will be performed prior to the initial assessments. Subjects who cannot be adequately trained and are not able to complete the W-B PRS are eligible for participation in the study and will not perform these assessments. Subjects 4 and 5 years of age who are not trainable in pFAB and lip/tongue palpation procedure will not be eligible for participation in the study.

#### 6.1.3 Baseline Evaluations (Day 1)

Prior to local anesthetic:

- Medical/dental history and concurrent illness (update if Day 1 is different from day of screening evaluation)
- pFAB
- Sensation rating by lip/tongue palpation procedure
- Record concomitant medications taken within 24 hours of local anesthetic administration

Confirm the following for subjects 4 and 5 years of age who are trainable in pFAB and standardized lip/tongue palpation procedure:

- Normal pFAB (smiling, speaking, drinking and drooling)
- Sensation of lip in the quadrant of the dental procedure is normal
- No opioid or opioid-like analgesics within 24 hours

## 6.2 PERIOD 2 - Anesthetic Administration and Dental Procedure (Day 1)

### 6.2.1 Anesthetic Administration

Immediately prior to administration of local anesthetic:

- Obtain vital signs (blood pressure and pulse) in sitting or supine position
- General Oral Cavity Assessment
- Start nitrous oxide and/or apply topical anesthetic, if used (20% benzocaine topical gel)

At administration of local anesthetic:

- Administer local anesthetic (lidocaine 2% with 1:100,000 epinephrine only).
  - Subjects 2 and 3 years of age and weighing ≥ 10 kg and < 15 kg will receive ¼ cartridge of local anesthetic
  - Subjects 2 to 5 years of age and weighing ≥ 15 kg and < 30 kg will receive ½ cartridge of local anesthetic
  - Subjects 2 to 5 years of age and weighing ≥ 30 kg will receive ½ cartridge or one full cartridge of local anesthetic

If pulpal anesthesia is insufficient to begin the dental procedure and the subject requires repeat injection at the same site(s) to induce pulpal anesthesia, then the subject is not eligible. However, a supplemental injection at an alternate site that does not result in soft tissue anesthesia is permitted, as follows:

  - Supplemental injections of lidocaine 2% with 1:100,000 epinephrine may be used as long as they are less than a total of 0.6 mL local anesthetic

- Record volume of local anesthetic, type of injection (nerve block, infiltration), and time that injection was completed, and whether supplemental injections were required.

Immediately after administration of local anesthetic:

- W-B PRS for pain of injection
- Specific Oral Cavity Assessment at the injection site(s)

### 6.2.2 Dental Procedure

- Perform restorative procedure. The dental procedure may be done by the Investigator who administered the local anesthetic or another person with the legal authority to perform the dental procedure.
- Complete the dental procedure within 60 minutes of the administration of local anesthetic

- Record stop time of dental procedure
- Record concomitant medications
- Update concurrent illness record

### 6.3 PERIOD 3 - Study Drug Administration (Day 1)

Confirm Subject is Eligible for Randomization

- Dental procedure was completed within 60 minutes of first administration of local anesthetic
- Subject has at least one abnormal pFAB test (smiling, speaking, drinking or drooling) at the completion of the dental procedure AND/OR has numbness of the (upper or lower) lip on the side of the dental procedure
- For subjects 2 and 3 years of age and weighing ≥ 10 kg and <15 kg, not more than ¼ cartridge of local anesthetic (excluding supplemental injections of lidocaine 2% with 1:100,000 epinephrine) was used
- For subjects 2 to 5 years of age and weighing ≥ 15 kg and < 30 kg, not more than half a cartridge of local anesthetic (excluding supplemental injections of lidocaine 2% with 1:100,000 epinephrine) was used
- For subjects 2 to 5 years of age and weighing ≥ 30 kg, not more than a whole cartridge of local anesthetic (excluding supplemental injections of lidocaine 2% with 1:100,000 epinephrine) was used
- For subjects undergoing a mandibular procedure, required an inferior alveolar nerve block to perform the dental procedure
- No local anesthetic other than lidocaine 2% with 1:100,000 epinephrine was used to perform the dental procedure
- No general anesthetics, sedatives (except nitrous oxide), opioids or opioid-like analgesics were administered during dental procedure

#### 6.3.1 Randomization to Study Drug

At randomization to OraVerse or sham:

Eligible subjects will be randomly assigned by IVRS to OraVerse or sham injection in a 2:1 ratio, stratified by location of the procedure (mandible, maxilla) and number of local anesthetic cartridges used (¼, ½ or 1 cartridge)

- Record time of randomization
- Record unique subject identification number
- W-B PRS of side of dental procedure
- General Oral Cavity Assessments (injection/procedure sites)

### 6.3.2 Administration of Study Drug

Prior to administration of study drug (OraVerse or sham):

- Obtain vital signs (blood pressure and pulse) in sitting or supine position
- Place visual barrier over the subject's eyes prior to study drug preparation and administration

At administration of study drug:

- The Investigator who administered the local anesthetic will administer the study drug (OraVerse or sham) using the same location(s) and same technique(s) used for the administration of local anesthetic
- Record completion time of study drug administration
- Subjects who received ¼ cartridge of local anesthetic for the dental procedure will receive ¼ cartridge of OraVerse by submucosal injection or one sham injection
- Subjects who received ½ cartridge of local anesthetic for the dental procedure will receive ½ cartridge of OraVerse by submucosal injection or one sham injection
- Subjects who received one cartridge of local anesthetic for the dental procedure will receive one cartridge of OraVerse by submucosal injection or one sham injection
- The sham injection will be performed without making an actual injection at the local anesthetic site, and will mimic the time, preparation and application using a comparable dental tool and technique.
- Supplemental injections of lidocaine 2% with 1:100,000 epinephrine will not be followed with OraVerse or sham injection
- Return used cartridge(s) to the kit and seal closed with tamper evident labels before removing visual barrier from subject
- Record concomitant medications
- Record any adverse events after study drug administration

## 6.4 PERIOD 4 - Observation (Day 1)

All subjects will be monitored at the site after the administration of study drug (OraVerse or sham) according to assessments and specific time points detailed below and in Appendix B. The observation period for safety and efficacy assessments will be 2 hours in all subjects.

The Investigator who administered the local anesthetic and study drug is unblinded to the randomization assignment and will not perform subsequent assessments during the observation period. A blinded observer will be responsible for making safety and efficacy assessments. The Principal Investigator at the site has responsibility to maintain optimal study conduct and supervision of the protocol.

Immediately after administration of OraVerse or sham:

- Remove the visual barrier from the subject
- For subjects receiving nitrous oxide, discontinue the sedative and administer oxygen for 5 minutes
- Obtain W-B PRS to assess pain at the injection site
- Perform pFAB
- Perform sensation rating by lip/tongue palpation procedure
- Conduct General Oral Cavity Assessment
- Obtain blood pressure and pulse; record position as sitting or supine

***Safety Assessments***

Safety assessments will be performed for all subjects at the timepoints specified below with an acceptable variation of ± 5 minutes unless specified otherwise.

- W-B PRS for pain of injection immediately after study drug administration (trainable subjects only)
- W-B PRS for pain in the mouth on the side of the procedure every 30 minutes post study drug for two hours; and prior to analgesics, as needed (trainable subjects only)
- Blood pressure and pulse in supine or sitting position at 15, 30, 60 and 120 minutes and prior to discharge
- Specific oral cavity assessments of the injection and procedure site(s) at 15, 30, 60 and 120 minutes and prior to discharge
- General oral cavity assessment prior to discharge
- Record any adverse events from time of study drug administration throughout the observation period. In addition, question the subject every half hour for adverse events and prior to discharge
- Concomitant medications taken during the observation period, including any analgesics taken for intraoral pain, medications previously prescribed (subject's parents/legal guardian will supply the medications), and medications required to treat an adverse event
- Schedule telephone and in-clinic follow-up appointments
- Discharge subject at the end of the observation period; record time of discharge

***Efficacy Assessments***

Efficacy assessments will be performed for subjects 4 and 5 years of age who are trainable in pFAB and standardized lip/tongue palpation procedures at the timepoints specified below with an acceptable variation of ± 5 minutes

- Sensation rating by lip/tongue palpation every 15 minutes for 2 hours after completion of study drug administration starting at 15 minutes after study drug administration

***In addition to these assessments:***

- Allow subjects access to oral liquids (at room temperature) using a straw

- Allow subjects access to soft foods that do not require chewing (such as pudding, yogurt, apple sauce) after lip/tongue sensation has returned to normal
- Allow ibuprofen if an analgesic is needed for intraoral or mouth pain; administer acetaminophen if the subject is intolerant or allergic to ibuprofen; record pain as an adverse event, record dose and time analgesic was administered and obtain W-B PRS prior to administration (if subject is trainable in W-B PRS)

### 6.5 PERIOD 5 - Telephone Follow-up (Days 1)

- Contact parent/legal guardian by telephone on Day 1; if subject or parent/legal guardian is not available at the scheduled time, make one more attempt to establish telephone contact later on Day 1. If unable to contact the subject by the end of Day 1, document on the Comments CRF
- Ask parent/legal guardian about intraoral pain, accidental injury (e.g., tongue or cheek biting), nerve injury, and analgesics taken for intraoral pain after leaving the study site; record responses on appropriate CRF
- Record adverse events and concomitant medications
- Record date and time of telephone follow-up

### 6.6 PERIOD 6 – In-clinic Safety Follow-up (Day 2 or 3)

- Adverse events including nerve injury, accidental injury and pain, concomitant medications, and general and specific oral cavity assessment to be performed at the study site by a treatment-blinded investigator. It can be conducted on either Day 2 or 3
- If the in-clinic safety follow-up is not conducted, document the reason on the Comments section of the CRF

# 7. ADVERSE EVENTS AND MANAGEMENT OF TOXICITY

## 7.1 Adverse Events

All AEs encountered after the study drug administration will be recorded on the CRF and reviewed by the Medical Monitor. Adverse events are defined in the International Conference on Harmonisation (ICH) Guidance for Industry E6: Good Clinical Practice as follows:

> An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH April 1996).

An AE is any adverse change from the subject's baseline condition, whether the adverse event is considered related to the study drug or not. AEs that occur during the study will be followed until resolution or the condition is stable. This may require obtaining blood or urine samples or performing clinical evaluations.

## 7.2 Serious Adverse Events

A serious adverse event (SAE), as defined in 21 CFR 312.32 is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death;
- a life-threatening adverse drug experience;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant disability/incapacity; or
- a congenital anomaly/birth defect.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The SAE (regardless of relationship to investigational product) reporting procedure is summarized:

- Complete and fax the "Serious Adverse Event Report" form to Novocol within 24 hours of the Investigator's knowledge of the SAE, even if all information regarding the SAE is unknown or incomplete, and discuss with the Medical Monitor, if needed

- File follow-up reports to Novocol and discuss with the Medical Monitor, as needed, with results of evaluation, treatment and course, copies of hospital reports, autopsy reports, discharge summaries, and other documents
- Report any fatal or life-threatening SAE that occurs on study immediately
- Report any death of a subject who dies within 30 days of administration of study drug
- Report any SAE to the IRB for the site, as required
- If the Investigator becomes aware of an SAE that occurs after the follow up visit and within thirty (30) days after dosing is completed, the same procedure will be used

### 7.3 Severity of Adverse Events

Adverse events will be graded according to the criteria in the WHO Toxicity Scale (Appendix F). Clinical adverse events not classified by this scale will be categorized using the following definitions:

**Mild**: discomfort noted, but no disruption of normal daily activity

**Moderate:** discomfort of sufficient severity to reduce or adversely affect normal activity

**Severe**: incapacitating, with inability to perform normal daily activity

### 7.4 Relatedness of Adverse Events

The Investigator must determine whether the AE is best described as unrelated, possibly related or related to study drug according to the following definitions:

**Unrelated:** There is evidence that the adverse event definitely has an etiology other than the assigned study drug.

**Possibly Related:** The adverse event has a temporal relationship to study drug administration. However, an alternative etiology may be responsible for the adverse event. Information on drug/product withdrawal may be lacking or unclear.

**Probably Related:** The adverse event has a temporal relationship to study drug administration. The event is unlikely to be related to an alternative etiology. There is a reasonable response on withdrawal (dechallenge). Rechallenge information is not required.

**Related:** The adverse event has a temporal relationship to study drug administration and resolves when the drug is discontinued. An alternative etiology is not apparent. If the subject is rechallenged with the assigned study drug, the adverse event recurs. Rechallenge is not necessarily required.

**Unknown:** Insufficient information to determine/assess relationship to the study drug.

The Investigator is required to provide details of the AE/SAE. An AE, whether serious or not serious, is designated unexpected if it is not reported in the clinical safety section of the Investigator's Brochure (IB) or if the event is of greater frequency, specificity, or severity than what is mentioned in the IB.

### 7.5 Management of Toxicity Related to Study Drug

There is no specific antidote for phentolamine in the event of overdose. Although an overdose of the study drug without any clinical sign or symptom is not technically an AE, it should be captured on the AE page of the CRF. Overdose is considered unlikely to occur in this study given the dose of phentolamine and route of administration.

If a hypersensitivity reaction occurs during the administration of study drug, the Investigator will discontinue the administration of study drug and provide general supportive measures. If an adverse event occurs after administration of study drug, the Investigator will provide general supportive measures.

General supportive measures include, but are not limited to, placing subject in supine position, administering oxygen, and administration of antihistamines and/or epinephrine. If symptoms progress or persist, or if epinephrine is administered, the Investigator will contact emergency medical services (call 911 or analogous number).

If a medical emergency occurs that requires unblinding to determine appropriate treatment, the Investigator will notify the Sponsor and Sponsor's Medical Monitor within 24 hours.

### 7.6 Withdrawal from Study Due to Adverse Event

Subjects withdrawn from the study due to adverse events will be followed by the Investigator until resolution or the condition has stabilized with all information documented on the CRF and source documentation. Subjects withdrawn due to adverse events or discontinued from the study will be required to complete the remaining safety assessments and followed by the Investigator until resolution or the condition has stabilized. Additional reports will be provided to the Sponsor or regulatory authorities as appropriate to document the AE.

# 8. STATISTICAL CONSIDERATIONS

## 8.1 Endpoints

### 8.1.1 Primary Endpoints

The primary objective of this study is the safety and tolerability of OraVerse in pediatric dental subjects 2 to 5 years of age undergoing mandibular or maxillary procedures:

The safety and tolerability of OraVerse will be evaluated based on the following parameters:

- incidence and severity of adverse events
- clinically significant changes in vital signs (blood pressure and pulse)
- clinically significant changes in oral cavity assessments
- nerve injury
- analgesics required for intraoral pain

The timing and sequence in which the above tests and assessments are to be performed are described in Section 6. The planned method of analysis of each safety and tolerability parameter is described in Sections 8.4 and 8.7.2.

### 8.1.2 Secondary Endpoints

Secondary objectives of this study will be evaluated on the following parameters in subjects 4 and 5 years of age who are trainable in W-B PRS, pediatric functional assessment battery (pFAB) and standardized lip/tongue palpation procedures:

- to evaluate the safety and tolerability of OraVerse as measured by incidence, severity and duration of intraoral pain as measured by W-B PRS
- to determine if OraVerse accelerates the time to normal function as measured by a pediatric Functional Assessment Battery (pFAB)
- to determine if OraVerse accelerates the time to normal lip sensation as measured by standardized lip palpation procedure
- for mandibular procedures, to determine if OraVerse accelerates the time to normal tongue sensation as measured by standardized lip palpation procedure

The timing and sequence in which the above tests are to be performed are described in Section 6. The determination of each endpoint and corresponding planned method of analysis are described in Sections 8.4, 8.7.2 and 8.7.3, respectively.

## 8.2 Randomization and Stratification

Approximately 150 subjects 2 to 5 years old will be enrolled into this study according to Table 4. Subjects will be randomized to OraVerse or sham in a 2:1 ratio resulting in 100 subjects receiving OraVerse and 50 subjects receiving a sham injection. It is planned that 15 subjects will

be enrolled in each of the 2 and 3 year old age groups and 60 subjects in each of the 4 and 5 year old age groups.

Randomization will be stratified by location of procedure (mandible or maxilla) and number of local anesthetic cartridges used (¼, ½ or 1 cartridge).

An Interactive Voice Response System (IVRS) will be utilized to ensure the appropriate ratio of each of these stratification factors between the two treatment groups.

### 8.3 Sample Size Determination

The primary objective of this study is the safety and tolerability of OraVerse in 2 to 5 year old subjects undergoing mandibular or maxillary dental procedures; thus, the sample size justification for this study is based on the probability of detecting potential adverse events that might occur during this study in the OraVerse treatment group. This study is not powered to detect treatment differences in the secondary efficacy endpoints.

If 100 subjects are enrolled in the OraVerse arm of the study, there will be a 95% confidence level of observing at least one occurrence of a specific adverse event given the true proportion of subjects that would develop this adverse event in the population is 3% (Louis T.A., 1981).

### 8.4 Definitions

#### 8.4.1 Study Drug

Study drug is defined as OraVerse (phentolamine mesylate) or sham injection.

#### 8.4.2 Randomization

A subject is considered randomized once the subject has been assigned a study kit that contains cartridges of OraVerse or empty cartridges for administration of the sham injection.

#### 8.4.3 Age

The subject's age is calculated as the number of years from the subject's date of birth to the randomization date, rounded down to the nearest integer:

Age = Integer ([Randomization Date - Date of Birth] / 365.25)

#### 8.4.4 Baseline

Unless specified otherwise, baseline represents the procedure or assessment done immediately before the administration of study drug.

For purposes of evaluating changes in selected safety and tolerability parameters (including vital signs and oral cavity assessments) relative to the subject's condition before administration of the local anesthetic and before the administration of study drug, two baselines will be defined.

The first baseline will be determined from the assessments done immediately before the administration of the local anesthetic; the second baseline will be determined from the assessments done immediately before the administration of study drug.

### 8.4.5 Time to Normal Pediatric FAB (pFAB)

The time to return of normal function is calculated by the number of minutes elapsed from the administration of study drug to the first of two consecutive assessments of the observer rating of smiling, speaking, drinking, and drooling as normal or not present. The return of normal function is also considered to occur in the event all functional tests are rated as normal or not present for the subject's last functional assessment battery and one or more of these tests from the preceding assessment are rated as other than normal (i.e., not done, abnormal, or present). Subjects who do not meet these criteria before the end of the 2-hour observation period will be right-censored at the last time the subject completed the pediatric functional assessment battery and none of the individual observer rated assessments are missing.

### 8.4.6 Time to Recovery of Normal Lip Sensation

The time to recovery of normal lip sensation is calculated by the number of minutes elapsed from the administration of study drug to the first of two consecutive reports of normal sensation of the upper or lower lip. The recovery of normal lip sensation is also considered to occur in the event the lip sensation test is rated normal at the subject's final evaluation and the rating from the preceding assessment is rated other than normal (i.e., not done or numb etc.). Subjects who do not meet these criteria before the end of the 2-hour observation period will be right-censored at the time of the subject's last sensation rating of the upper or lower lip by palpation.

### 8.4.7 Time to Recovery of Normal Tongue Sensation (Mandibular Procedures)

The time to recovery of normal tongue sensation is calculated by the number of minutes elapsed from the administration of study drug to the first of two consecutive reports of normal sensation of the tongue. The recovery of normal tongue sensation is also considered to occur in the event the tongue sensation test is rated normal at the subject's final evaluation and the rating from the preceding assessment is rated other than normal (i.e., not done or numb, etc). Subjects who do not meet these criteria before the end of the 2-hour observation period will be right-censored at the time of the subject's last sensation rating of tongue by palpation.

## 8.5 Analysis Subsets

The analysis sets described in this section will serve as the data sources for the analyses of safety and the secondary efficacy endpoints.

The analysis of the safety and tolerability endpoints will be performed in accordance with the safety analysis data set principle. The exception will be the Wong-Baker FACES Pain Rating Scale which will be only for subjects 4 and 5 years of age.

For subjects 4 and 5 years of age, the secondary efficacy endpoints of pediatric FAB (pFAB) and time to recovery of normal lip and tongue sensation will be performed in accordance with

the modified intent-to-treat (mITT) principle. The modified intent-to-treat analysis set for these endpoints are described in detail in Section 8.5.2.

### 8.5.1 Safety Analysis Set

The safety analysis set is defined as:

- all randomized subjects who are administered study drug
- For the Wong-Baker FACES Pain Rating Scale: all randomized subjects 4 and 5 years of age who were trainable in the completion of W-B PRS and administered study drug

Subjects will be grouped in the safety analysis set according to which study drug was actually administered.

### 8.5.2 Modified Intent-to-Treat Analysis Set

The following mITT analysis sets are defined as follows:

- the mITT pFAB analysis set includes all randomized subjects 4 to 5 years of age who were trainable in pFAB, have normal pFAB at baseline prior to administration of local anesthetic, and have at least one abnormal function (smiling, speaking, drinking, or drooling) at completion of the dental procedure as rated by the observer.

- the mITT Lip Sensation analysis set includes all randomized subjects 4 to 5 years of age who were trainable in standardized lip/tongue palpation procedure, have normal lip sensation at baseline prior to administration of local anesthetic, and have numbness of the relevant lip quadrant at completion of the dental procedure.

- the mITT Tongue Sensation analysis set includes all randomized subjects 4 to 5 years of age who were trainable in standardized lip/tongue palpation procedure, have normal tongue sensation at baseline prior to administration of local anesthetic, and have numbness of the tongue at completion of the dental procedure.

Subjects will be grouped in the mITT analysis set according to their randomized study drug assignment, irrespective of which one is actually administered (if any).

## 8.6 Interim Analysis

No formal interim analysis of this study is planned. However, a safety review using blinded data will be performed by the Medical Monitor after 30 subjects have completed the study. The safety and tolerability of OraVerse will be evaluated based on the following parameters:

- incidence and severity of adverse events
- clinically significant changes in vital signs (blood pressure and pulse)
- clinically significant changes in oral cavity assessments
- nerve injury

- analgesics required for intraoral pain

## 8.7 Statistical Methods of Analysis

### 8.7.1 General Principles

The primary objective of this Phase 4 pediatric study is to assess the safety and tolerability of OraVerse based on the safety analysis data set defined in Section 8.5.1. Descriptive statistics will be utilized to characterize the safety and tolerability profile of OraVerse as compared to the sham injection. Because the sample size of this study is based on enrolling an adequate number of subjects to detect potential adverse events in the OraVerse treatment, formal inferential statistical methodologies are not appropriate given this study's objectives, study design and number of primary safety endpoints.

The statistical analysis of each of the secondary efficacy endpoints are based on the corresponding mITT analysis set defined in Section 8.5.2. These secondary endpoints are exploratory in nature and not adequately powered to detect statistically significant differences in treatment group comparisons. Descriptive statistics employing Kaplan-Meier methods will be utilized to characterize time to normal sensation of the lip and tongue for each treatment group. In addition, inferential statistical methodologies using the stratified log-rank test will be employed to help characterize the robustness of the trends seen between the treatment groups. These inferential statistical methods on secondary efficacy endpoints are not intended to make definitive claims of efficacy, rather to identify potential trends within these efficacy endpoints.

While this study is not adequately powered for treatment group comparisons of the secondary efficacy endpoints, additional mITT analysis will be conducted in order to evaluate the robustness of the results based on the secondary efficacy analysis. These analyses may include, but are not limited to comparisons between treatment groups based on the proportion of subjects achieving normal sensation by the end of each half hour during the planned observation period (i.e. ½, 1, 1 ½, 2 hours) and the randomization stratification variables.

Hypothesis testing of the secondary efficacy endpoints will be performed using a two-sided significance level of 0.05.

### 8.7.2 Safety Analysis

Unless otherwise specified, the safety tabulations will be summarized by:

- Age group (2, 3, 4, and 5 years of age)
- Location of procedure (mandible or maxilla)
- Amount of local anesthetics used (¼, ½ , or 1 cartridge)
- Overall (pooled across all factors and study sites)

Adverse events will be coded to preferred terms and system organ classes according to the Medical Dictionary for Regulatory Activities (MedDRA®). The severity of each adverse event will be determined by the investigator from the WHO Toxicity Criteria (Appendix F) or by protocol

defined criteria as outlined in Section 7.3. The incidence of adverse events will be summarized by treatment group according to preferred term and system organ class. Tabulations of adverse events by severity grade and causal relationship to study drug also will be provided. The duration and outcome of each adverse event will be reported in subject listings.

Vital sign results (blood pressure and pulse) will be summarized by treatment group at each of the protocol specified assessments by calculating the mean, standard deviation, median, and range. In addition, the number and proportion of subjects in each treatment group who meet one or more of the following criteria will be reported:

- Decrease in systolic blood pressure (supine or sitting) of >20 mm Hg on two consecutive measurements after the administration of study drug relative to the baseline systolic blood pressure
- Decrease in diastolic blood pressure (supine or sitting) of >20 mm Hg on two consecutive measurements after the administration of study drug relative to the baseline diastolic blood pressure
- Increase in pulse (supine or sitting) of 20 bpm on two consecutive measurements after the administration of study drug relative to the baseline pulse

For purposes of this analysis, two reference values will be used for baseline; the result measured just before the administration of local anesthetic and the result measured just before the administration of study drug. Separate tabulations will be provided for each reference baseline value.

Clinically significant abnormalities in oral cavity assessments will be summarized by treatment group for each of the protocol specified assessments by calculating the number and proportion of subjects who experience complications in the mouth, at the dental procedure site(s), and at the injection site(s) of local anesthetic and study drug.

Analgesic requirements will be summarized by the number and proportion of subjects who take at least one analgesic for the treatment of intraoral pain during the 2-hour observation period following the administration of study drug. Use of analgesics during the approximate 24-hour period after dismissal from the dental clinic will also be tabulated. The administration of concomitant medications, including analgesics, will be tabulated by medication class and by drug dictionary term within medication class according to the WHO Drug dictionary.

Nerve injuries, if any, will be tabulated by treatment group.

For subjects 4 and 5 years of age, the incidence, severity, and duration of intraoral pain will be primarily evaluated using the W-B PRS. Each W-B PRS score will be classified into one of four mutually exclusive severity categories such that the number and proportion of subjects reporting no pain, mild pain, moderate pain, or severe pain can be evaluated clinically. No pain corresponds to Face 0 (no hurt) on the W-B PRS. Mild pain is defined as Face 1 and includes the descriptor "hurts a little bit". Moderate pain is defined as Face 2 or Face 3 and includes the descriptors "hurts a little more" and "hurts even more". Severe pain is defined as Face 4 or Face 5 and includes the descriptors "hurts a whole lot" and "hurts worse". The intraoral pain associated with W-B PRS greater than Face 1 will be considered clinically significant in the

treatment setting under evaluation. Of special interest is a comparison of the W-B PRS severity scores reported immediately after the administration of study drug. A comparison between treatment groups also will be made for the maximum W-B PRS severity score reported during the 2-hour observation period after the administration of study drug to determine if OraVerse is associated with increased pain relative to the sham injection which may be consistent with an acceleration in the time to the return of normal sensation following the completion of the dental procedure.

### 8.7.3 Efficacy Analysis

The time to normal function (pFAB) will be summarized descriptively by treatment group using the Kaplan-Meier method. The estimated median for each treatment group and corresponding 95% confidence interval will be reported. The stratified log-rank test will be used to test the null hypothesis that the distributions for the time to recovery of normal sensation of the lip are equal between the two treatment groups versus the alternative hypothesis that distributions are different. The location of dental procedure (mandibular and maxillary) stratification factors will be used for computing the stratified log-rank test statistic.

The above methods of analysis will also be used on the time to recovery of normal sensation of the lip and tongue.

### 8.7.4 Missing Data

Based on the nature of the study and previous studies by the sponsor involving local anesthetics, the amount of missing data expected is minimal. In general, all analyses will use observed data as received from the clinical database. Missing values will not be imputed except the last post-baseline observation carried forward (LOCF) method will be used to impute missing item responses for the Wong-Baker FACES PRS and the pediatric Functional Assessment Battery (pFAB) scores.

# 9. RESPONSIBILITIES

## 9.1 Investigator Responsibilities

### 9.1.1 Compliance with Good Clinical Practice

The Investigator will print name and sign the Investigator Signature Sheet.

The Investigator will ensure adherence to the basic principles of "Good Clinical Practice," as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, part 54, and part 56, as well as the International Conference on Harmonisation (ICH) Guideline of Good Clinical Practice (ICH E6) and the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

The Investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki", ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the subject.

### 9.1.2 Institutional Review Board (IRB)

The Investigator will submit this protocol and any materials (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent/assent) to the IRB. Approval from the IRB must be obtained before starting the study and documented in a letter to the Investigator specifying the protocol number, protocol version, documents reviewed, and date on which the IRB granted the approval.

The Investigator will submit all SAE reports to the IRB within the locally specified time requirement. The Investigator will submit any safety report from the Sponsor to the IRB within the locally specified time requirement. The Investigator is responsible for submitting all protocol amendments to the appropriate IRB prior to implementation.

### 9.1.3 Informed Consent/Assent

The Investigator will obtain verbal or written assent from those subjects capable, and as appropriate, and obtain written informed consent from one parent or legal guardian of each participant if consistent with IRB policy and state law after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures. The Investigator will utilize IRB-approved consent forms.

Each informed consent form will be signed and dated by the parent or legal guardian of the subject, and the person obtaining the informed consent. By signing the informed consent, the parent or legal guardian agree that the subject will complete all evaluations unless the parent or legal guardian withdraws consent or the subject is withdrawn from the study for any reason.

As part of the informed consent process, the Investigator will obtain HIPAA compliant authorization from parent or legal guardian to use and disclose relevant protected health information (PHI) and permission for authorized representatives of Novalar, or regulatory

authorities including the FDA, to review in confidence any records identifying subjects in the clinical study.

Recruitment efforts may precede obtaining informed consent and assent; however, informed consent and assent must be obtained prior to any protocol specific procedures being performed.

The Investigator will communicate any new information on safety to the parent(s) or legal guardian(s) who consent for their child to participate in this study in accordance with IRB requirements. The informed consent and assent form will be updated, if necessary.

### 9.1.4 Confidentiality

The Investigator will assure that subjects' anonymity will be strictly maintained and that their identities will be protected from unauthorized parties. Only subject initials and an identification code (i.e., not names) will be recorded on any form submitted to the Sponsor or IRB.

The Investigator agrees that all information received from Novocol Pharmaceutical of Canada, Inc., (Novocol) including but not limited to the Investigator's Brochure, this protocol, CRFs, the study drug, and any other study information, are the sole and exclusive property of Novocol. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Novocol.

The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

### 9.1.5 Study Files and Retention of Records

The Investigator will maintain adequate and accurate records that fully document the conduct of the study and enable study data to be verified. These documents should be classified into separate categories: 1) Investigator's study file and 2) subject clinical source documents.

- The Investigator's study file includes the original protocol, protocol amendments, CRFs and query forms, IRB approval with correspondence, approved informed consent and assent forms, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

- Subject clinical source documents include, but are not limited to, the subject's medical/dental records, laboratory and x-ray reports, electrocardiograms (ECGs), pathology and special assessment reports, consultant letters, screening and enrollment log, as applicable.

The Investigator will make the source documents for this study available to Novocol or its representatives, or to regulatory or health authority inspectors. The Investigator will retain all study documents for at least 3 years after the study close-out visit. The Investigator may retain documents longer if required by applicable regulatory requirements or by agreement with Novocol Pharmaceutical of Canada, Inc.

The Investigator will notify Novocol Pharmaceutical of Canada, Inc. prior to destroying any study records. Should the Investigator wish to assign the study records to another party or move them to another location, the Investigator must notify Novocol Pharmaceutical of Canada, Inc. in writing in advance. If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements will be made between the Investigator and Novocol Pharmaceutical of Canada, Inc. for storage. If source documents are required for continued care of the subject, appropriate copies for storage off site will be made.

### 9.1.6 Case Report Forms

The Investigator is responsible for the completeness and accuracy of information collected on the CRFs for each individual enrolled. The Investigator will review and approve all CRFs; document the reason that a subject withdraws from the study on the appropriate CRF and attempt to obtain termination assessments; and continue follow-up to document the outcome of any adverse event.

### 9.1.7 Drug Accountability

The Investigator is responsible for ensuring adequate accountability of all used and unused study drug, including acknowledgment of receipt of each shipment of study products (quantity and condition) and subject dispensing records. Dispensing records will document quantities received and quantities dispensed, lot number, date dispensed, Subject identifier number, and initials of the person dispensing the study drugs.

The Investigator will make these study drug accountability records available to the study monitor. At the end of the study and after the study monitor has completed drug accountability, study drug supplies will be returned for destruction, unless an alternative disposition is arranged and approved by the Sponsor.

### 9.1.8 Inspections

The Investigator will make the source documents for this study available to Novocol Pharmaceutical of Canada, Inc. or its authorized designee, or to the regulatory or health authority inspectors.

### 9.1.9 Protocol and IRB Compliance

The Investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. The Investigator will submit all amendments to the protocol to the IRB in accordance with local requirements. Approval by the IRB will be obtained before amendments are implemented.

## 9.2 Sponsor Responsibilities

Novocol Pharmaceutical of Canada, Inc. (Novocol) is the Sponsor of this study. Novocol or its designee is responsible for selecting qualified Investigators, providing them with information needed to conduct the study properly, monitoring the study to ensure it is conducted in

compliance with the Code of Federal Regulations, local/regional requirements, GCP guidelines, and the protocol, and reporting the new adverse events or risks to the Investigators, FDA and local regulatory authorities in a timely manner.

### 9.2.1 Protocol, Protocol Amendments, and Safety Updates

Novocol is responsible for the protocol and protocol amendments, except those intended to reduce immediate risk to subjects. Novocol is responsible for submitting the protocol and protocol amendments to the appropriate regulatory authorities.

Novocol is responsible for providing written safety updates to the Investigator. Safety updates include any information that significantly bears on the subject's risk to receive the study drug.

### 9.2.2 Monitoring of Study

Prior to the initiation of the study, Novocol or its designee will ensure the Investigator and study staff understands the investigational status of the product, all requirements of the protocol, and regulatory responsibilities as an Investigator. The study monitor will visit each clinical site at appropriate intervals to ensure compliance with the protocol and to verify accuracy and completeness of data reported, and accountability of supplies of investigational product.

The study monitor will be available for consultation with the Investigator and serve as a liaison between the site and the Sponsor. The study monitor or authorized representatives of the Sponsor may inspect all data, documents, and records required to be maintained by the Investigator including but not limited to, medical/dental records and pharmacy records for subjects participating in this study. The study site will permit access to such records.

### 9.2.3 Data Handling and Recording

Novocol or its authorized designee is responsible for data processing. The Investigator is responsible for the accurate and timely completion of CRFs. Completed CRFs will be reviewed for accuracy and completeness by study monitors. If necessary, the site will be contacted for corrections and/or clarifications. All data will be entered into a study database for analysis and reporting. Upon completion of data entry, the database will receive a quality assurance check to ensure acceptable accuracy and completeness.

### 9.2.4 Study Report and Publication

Novocol is responsible for submitting the study report to the appropriate regulatory authorities and for publishing the results of this study. No results will be published without prior review and approval by Novocol.
Within one year of the final clinical study report, the results of the entire study will be submitted for public disclosure in abstract, manuscript, or presentation form, under the guidance of a Study Publication Committee. Following that disclosure, Investigators in this study may communicate, orally present, or publish site specific results in scientific journals or other scholarly media. No such communication, presentation, or publication will include Novocol's confidential information.

Investigator(s) will submit any proposed publication or presentation to Novocol at least 45 days prior to submission of the publication or presentation. Investigator(s) will withhold publication or presentation for an additional 90 days in order to enable Novocol to obtain patent protection, if deemed necessary. These terms will hold except to the extent different period(s) may be provided for in the clinical study agreement between the parties, in which case such different time period shall control.

### 9.3 Joint Investigator / Sponsor Responsibilities

#### 9.3.1 Access to Information, Quality Control and Assurance

In accordance with International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines, the study monitor will have direct access to the Investigator's source documentation at regular intervals throughout the study, in order to document compliance with the protocol and verify the completeness and accuracy of the data recorded in the CRFs. The Investigator will cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved in a reasonable period of time.

Study monitors will periodically audit, at mutually convenient times during and after the study, all CRFs and corresponding office and clinical laboratory records for each subject. The monitoring visits provide Novocol with the opportunity to evaluate the progress of the study, to verify the accuracy and completeness of CRFs, to resolve any inconsistencies in the study records, and to assure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

#### 9.3.2 Withdrawal of Subjects

The subject may choose to withdraw from the study, or any parent or legal representative may choose to withdraw a subject from the study, for any reason and at any time. The Investigator will withdraw any subject if it is not in the subject's best interest to continue or the subject is not compliant with study assessments. When a subject is withdrawn from the study (regardless of the reason), the date and reason will be recorded. In addition, all evaluations specified for the end of the observation period will be performed, if feasible.

In addition, parent or legal representatives may choose to withdraw authorization to use and disclose their Protected Health Information (PHI) as defined by the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Such withdrawal of authorization must be made to the Investigator in writing. Any PHI collected by the Investigator or Sponsor prior to the date of such withdrawal will continue to be used and disclosed.
Subjects may be removed from the study if one or more of the following events occur:

- Significant protocol violation on the part of the Investigator;
- Significant noncompliance on the part of the subject;
- Withdrawal of consent (refusal of the subject or parent/legal guardian to continue treatment or assessments);
- Due to adverse event or unacceptable toxicity;
- Decision by the Investigator that termination is in the subject's best medical interest;

- Unrelated medical illness or complication;
- Lost to follow up.

### 9.3.3 Study Discontinuation

Both the Investigator and Novocol reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, both the Investigator and Novocol will assure that adequate consideration is given to the protection of the subjects' interests.

Subject's medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, Novocol's Medical Monitor (or designee), and the Institutional Review Board (IRB).

The information developed in this clinical study will be used by Novocol in the clinical development of the study drug. Novocol may disclose information to clinical Investigators, to other pharmaceutical companies, to the FDA and to other government agencies as required.

## 10. ETHICS

### 10.1 Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments, as described in Appendix G.

### 10.2 Institutional Review Board

The protocol, informed consent and assent, and any materials (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent/assent) for this study will be reviewed and approved by a duly constituted IRB.

The IRB is responsible for reviewing the protocol, informed consent/assent, Investigator's Brochure, all amendments, and periodic safety reports in accordance with current institutional, local, and national regulations. A letter documenting the IRB's approval of the protocol will be provided to the Sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

The Investigator will submit all periodic reports and updates that the IRB may require, including any final close out reports. The Investigator will inform the IRB of any reportable adverse events.

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## APPENDIX A: STUDY FLOW CHART

| Protocol Section | Study Period | Activity |
|---|---|---|
| Section 6.1 | PERIOD 1 - Screening<br>Day -14 to Day 1 | Obtain informed consent/assent<br>and conduct initial screening<br>↓ |
| | PERIOD 1: Screening<br>Day 1 | Subject training and baseline evaluations confirming eligibility<br>↓ |
| Section 6.2 | PERIOD 2 - Anesthetic Administration and Dental Procedure<br>Day 1 | Anesthetic administration, dental procedure<br>↓ |
| Section 6.3 | PERIOD 3 - Study Drug Administration<br>Day 1 | Confirm selection criteria; randomize to OraVerse or sham, and administer assigned study drug (OraVerse or sham), adverse events, concomitant meds<br>↓ |
| Section 6.4 | PERIOD 4 – Observation Period<br>Day 1 | Safety assessments: W-B PRS, vital signs, general and specific oral cavity assessments, adverse events, concomitant meds).<br>Efficacy assessments: pFAB and lip/tongue palpation |
| Section 6.5 | PERIOD 5 – Telephone Follow-ups<br>Day 1 | Adverse events, concomitant meds including analgesics, inquiries regarding pain, accidental injuries due to biting, nerve injury |
| Section 6.6 | PERIOD 6 – In-clinic Safety Follow-up<br>Day 2 or 3 | Adverse events, concomitant meds including analgesics, inquiries regarding pain, accidental injuries due to biting, nerve injury , general/specific oral cavity assessments |

## APPENDIX B: SCHEDULE OF ASSESSMENTS

| Assessment | Period 1<br>Screening<br>Day -14 to Day 1 | Period 2<br>Anesthetic/ Dental Procedure<br>Day 1 | Period 3<br>Study Drug Adminis-tration<br>Day 1 | Period 4<br>Obser-vation<br>Day 1 | Period 5<br>Telephone Follow-Up<br>Day 1 | Period 6<br>In-clinic Safety Follow-up<br>Day 2 or 3 |
|---|---|---|---|---|---|---|
| Informed Consent /Assent and Assign Scn. # | X | | | | | |
| Medical/Dental History/Concurrent Illness | X[a] | X[d] | | | | |
| Demographics (including height and weight) | X | | | | | |
| Training: W-B PRS, pFAB, lip and tongue palpation procedure in subjects age 4 and 5 | X[b] | | | | | |
| BP and pulse (supine or sitting) | | X[e] | X[i, j] | X[l] | | |
| Confirm interim eligibility | X[c] | | | | | |
| Apply Topical Anesthetic, if needed | | X[e] | | | | |
| Administer Local Anesthetic and record type of injection and time it is completed | | X | | | | |
| Dental Procedure and record stop time | | X | | | | |
| Randomize to Study Drug - record time and assign Subject ID # | | | X | | | |
| Place Visual Barrier for Blinding | | | X[i] | | | |
| Administer Study Drug and record time administration is completed | | | X | | | |
| Remove Visual Barrier | | | | X | | |
| Discontinue nitrous oxide (if given) and administer oxygen for 5 minutes | | | X | | | |
| pFAB – subjects age 4 and 5 years | X[b] | X[e] | X[g, j] | X[l] | | |
| Lip and tongue palpation - subjects age 4 and 5 | X[b] | X[e] | X[g, j] | X[l] | | |
| Confirm final eligibility | | | X[h] | | | |
| W-B PRS of local anesthetic injection | | X[f] | | | | |
| W-B PRS of study drug injection | | | X[j] | | | |
| W-B-PRS of side of dental procedure | | | X[g] | X[l] | | |
| General Oral Cavity Assessment | | X[e] | X[g, j] | X[l] | | X |
| Specific Oral Cavity Assessments (Injection/Procedure Sites) | | X[f] | | X[l] | | X |
| Concomitant Medications | X[k] | X | X | X[l] | X | X |
| Adverse Events | | | X | X[l] | X | X |
| Schedule Day 1 telephone safety follow-up | | | | X | | |
| Schedule in-clinic safety follow-up | | | | X | | |
| Discharge subject (record time) | | | | X | | X |

**Coding Legend for Assessment Time Points:**

a) Update during Evaluation on Day 1 if different from day of Initial Screening of Selection Criteria
b) Performed on Day 1
c) Normal lip sensation, no opioid or opioid-like analgesics within 24 hours
d) Update concurrent illness record, if necessary
e) Prior to administration of local anesthetic
f) After administration of local anesthetic
g) Prior to randomization to OraVerse or sham
h) In subjects 4 and 5 years of age who are trainable in pFAB and standardized lip/tongue palpation procedures, at least one abnormal pFAB test OR numbness of the lip on the side of the dental procedure at completion of dental procedure. For mandibular procedures, use of inferior alveolar nerve block to perform the procedure. For all subjects, dental procedure was completed within 60 minutes of administration of local anesthetic, amount of local anesthetic was consistent with weight; no opioid or opioid-like analgesics, sedatives except nitrous oxide), or local anesthetic other than lidocaine 2%/epinephrine was administered during dental procedure
i) Prior to preparation and administration of study drug
j) Immediately after administration of study drug
k) Record concomitant medications taken within 24 hours of local anesthetic administration
l) **Post Study Drug:**

*All subjects will be assessed for safety and efficacy during a 2-hour observation period. Subjects 4 and 5 years of age who are not trainable in W-B PRS will not perform these pain assessments.*

Safety assessments are performed at the timepoints specified below with an acceptable variation of ± 5 minutes unless specified otherwise.

W-B PRS for pain in the mouth on the side of the procedure every 30 minutes post study drug for two hours (all subjects); and prior to analgesics, as needed

Blood pressure and pulse in supine or sitting position at 15, 30, 60 and 120 minutes and prior to discharge

Specific oral cavity assessments of the injection and procedure site(s) at 15, 30, 60 and 120 minutes and prior to discharge

General oral cavity assessment prior to discharge

Adverse Events: Record any adverse events from time of study drug administration throughout the observation period. In addition, query the subject every 30 minutes for adverse events during the observation period, at discharge and at telephone and in-clinic follow-ups

Concomitant Medications: Medications taken during the observation period, including any analgesics taken for intraoral pain, medications previously prescribed (subject's parents/legal guardian will supply the medications), and medications required to treat an adverse event

*Efficacy Assessments in subjects 4 and 5 years of age*

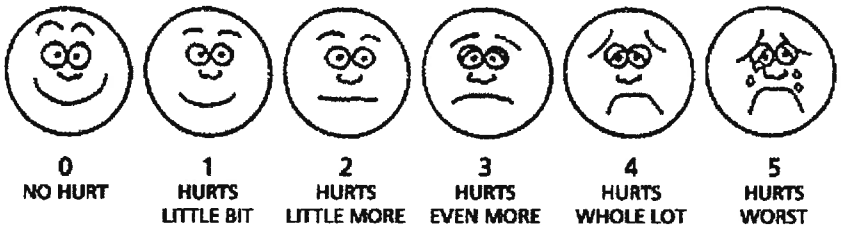
Efficacy assessments are performed at the timepoints specified below with a variation of ± 5 minutes

pFAB: every 15 minutes for 2 hours after study drug administration

Standardized lip/tongue palpation procedure: every 15 minutes for 2 hours after study drug administration

## APPENDIX C: WONG-BAKER FACES PAIN RATING SCALE

Pain will be rated by subjects 4 to 5 years of age using the Wong Baker FACES Pain Rating Scale. The subject will select one of six faces representing pain intensity.




**Instructions:**

- Point to each face using the words to describe the pain intensity.
- Explain that each face is for a person who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain.
  - Face 0 is very happy because he doesn't hurt at all.
  - Face 1 hurts just a little bit.
  - Face 2 hurts a little more.
  - Face 3 hurts even more.
  - Face 4 hurts a whole lot.
  - Face 5 hurts as much as you can imagine, although you don't have to be crying to feel this bad.
- Explain that the sad faces represent pain – not the unpleasantness of numbness or being at the dentist
- Ask the subject to choose the face that best describes their own pain and record the appropriate number.

## APPENDIX D: FUNCTIONAL ASSESSMENT BATTERY AND INSTRUCTIONS

Four functions will be tested in a standardized sequence at specified times in the protocol: smiling, speaking, drinking, and drooling.

- Smiling, speaking, and drinking will be rated as normal or abnormal by a blinded observer
- Drooling will be rated as present or absent by the blinded observer (actually observed).

**Definitions:**

- Normal for each function will be defined as same as or equivalent to performance of test prior to dental procedure (baseline)
- Abnormal for each function will be defined as not normal, i.e., different from baseline; examples are given under instructions for rating of each test
- Presence of drooling will be interpreted as abnormal for that function
- "Normal function" will be defined as normal ratings for all four functions
- "Abnormal function" will be defined as one or more abnormal ratings

**Overall instruction:** "These tests are meant to look at how the medicine that your doctor gave you today to work on your tooth (teeth) will affect you".

**Smiling Test**

Ask the subject to give you a smile. Encourage the subject to smile with age appropriate tools such as smiling faces, etc.

Rating by observer: look for symmetry; rate any asymmetry as abnormal

**Speaking Test**

Instruct the pediatric subject to repeat the words out loud that you will read to them. Repeat the word if the subject does not reply the first time read. Read each word separately from the list below and with pause for the subject to repeat it back before reading the next word.

| |
|---|
| 1. mouth |
| 2. feather |
| 3. leaf |
| 4. balloon |
| 5. bus |
| 6. toes |
| 7. chair |
| 8. watch |
| 9. pages |
| 10. car |

Rating by observer: listen for articulation of words or speech sounds; words containing "r", "l" and "s" are often affected; if certain words or speech sounds are slurred or not understandable, circle those words on the source document and rate as abnormal.

**Drinking Test**

Instruction to subject: "Drink this beverage from this cup". Encourage drinking by using something that the subject likes (room temperature juice, soda, etc).

Rating by observer: observe drinking and then observe for 1 additional minute; rate any cough, choking, or interruption to breathe as abnormal; rate any leakage or spillage as abnormal under drooling.

**Drooling Test**

Instruction to subject: "I will observe you for drooling while you are here at the dentist's office"

Rating by observer: rate the presence of drooling that is observed as abnormal under the observer rating; be especially aware of the period immediately following the drinking test; rate any reported presence of drooling within 15 minutes as abnormal under the subject rating.

## APPENDIX E: INSTRUCTIONS FOR SENSATION RATING

Guidance to the investigator is in bold type. Instructions for the observer to convey to the subject are in normal type.

**A. Determine which quadrant of this subject's mouth will be anesthetized.**

The pediatric subject will be asked to rate the sensation in the (upper or lower) lip using terms for the equivalent of either numb or normal for their age group. Soft-tissue anesthesia rating of the pediatric subject will be determined with age appropriate terms such as "feels different", "numb", "funny", "fuzzy" or frozen"

Instruct the pediatric subject to tap his/her (upper or lower) lip by demonstrating it. Repeat the instructions before each assessment:

1. Use only the pad of your index or middle finger.
2. Use light pressure and always the same pressure. Don't press so hard that you push your lip flat against your teeth.
3. Tap your lips the same way each time you tap.
4. Tap to one side or the other rather than in the middle.
5. Tap 3 times in rapid succession

**B. At this point, show them what the pad of their finger is by circling the pad of your index finger with the tip of your other index finger while you explain that this is the finger pad.**

**C. Demonstrate the proper technique for tapping the upper or lower lip by touching your own lip 3 times using proper pressure and explain that this is the proper technique.**

**D. Demonstrate <u>improper</u> technique by pressing your upper or lower lip, as applicable against your teeth, holding that position so the subject can clearly discern what you are doing, as you explain that this is the wrong way to tap.**

"Later you will tell me how the (upper or lower) lip feels where the dentist did the work that you need to be done on your teeth. This part of your lip will feel different because of what the dentist is going to give you before starting to work on your teeth that it does not hurt. However, the other side of your mouth should not feel different and you may tap it to see how it feels."

Use words such as "feels different", "numb", "funny", "fuzzy", "frozen" etc. deemed appropriate to describe the abnormal sensation of the lip to elicit the information on the soft-tissue anesthesia status of the subject).

**At this time, demonstrate how you will tap the part of your (upper or lower) lip that will feel different. Now tap your (upper or lower) lip on the opposite side of your mouth.**

**E. Ask the subject to point to the quadrant of their mouth where the dental procedure will be performed and verify that their response is correct. If incorrect, teach the subject which is the proper quadrant and then ask them to demonstrate how they will tap the part of their upper or lower lip that will be numbed by the anesthetic. Repeat these instructions as necessary, but if they cannot correctly apply instructions 1 through 5 after five tries, they cannot be enrolled in the study.**

The anesthetic may also make your tongue feel different (again, use words such as "feels different", "numb", "funny", "fuzzy", "frozen" etc. to describe the numbness of the tongue). Tap your tongue in the same way you tapped your lip. Using the pad of your finger, tap the side of your tongue 3 times using the same light pressure. Don't tap the tip of your tongue. If you are tapping your lip on the left side, then tap the left side of your tongue. You may need to stick your tongue out to do this comfortably. You need not open your mouth wide to reach the side of your tongue.

Follow the instructions above each time you are asked. You will tap many times in the next few hours. You must use the same amount of pressure each time you tap.

## APPENDIX F: WORLD HEALTH ORGANIZATION TOXICITY SCALE (Greater than 3 months of age, November 2007)

| **LOCAL REACTIONS** | | | | |
|---|---|---|---|---|
| | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| Induration | < 10mm | 10-25 mm | 26-50mm | >50mm |
| Erythema | < 10mm | 10-25 mm | 26-50mm | >50mm |
| Edema | < 10mm | 10-25 mm | 26-50mm | >50mm |
| Rash at Injection Site | < 10mm | 10-25 mm | 26-50mm | >50mm |
| Pruritus | Slight itching at injection site | Moderate itching at injection extremity | Itching at injection extremity and other sites | Itching over entire body |
| **HEMATOLOGY** | | | | |
| | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| Hemoglobin for children greater than 2 years of age | 10-10.9 gm/dL | 7.0-9.9 gm/dL | <7.0 gm/dL | Cardiac Failure secondary to anemia |
| Absolute Neutrophil Count | 750-1200/$mm^3$ | 400-749/$mm^3$ | 250-399/$mm^3$ | <250/$mm^3$ |
| Platelets | ------- | 50,000-75,000/$mm^3$ | 25,000-49,999/$mm^3$ | <25,000/$mm^3$ |
| Prothrombin Time (PT) | 1.1-1.2 x ULN | 1.3 -1.5 x ULN | 1.6 -3.0 x ULN | >3.0 x ULN |
| Partial Thromboplastin Time (PTT) | 1.1-1.6 x ULN | 1.7-2.3 x ULN | 2.4 -3.0 x ULN | >3.0 x ULN |

| **GASTROINTESTINAL** | | | | |
|---|---|---|---|---|
| | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| Bilirubin (when accompanied by any increase in other liver function test) | 1.1 - <1.25 x ULN | 1.25 - <1.5 x ULN | 1.5 – 1.75 x ULN | > 1.75 x ULN |
| Bilirubin (when other liver function are in the normal range) | 1.1 - <1.5 x ULN | 1.5 - <2.0 x ULN | 2.0 – 3.0 x ULN | > 3.0 x ULN |
| AST (SGOT) | 1.1 - <2.0 x ULN | 2.0 – <3.0 x ULN | 3.0 – 8.0 x ULN | > 8 x ULN |
| ALT (SGPT) | 1.1 - <2.0 x ULN | 2.0 – <3.0 x ULN | 3.0 – 8.0 x ULN | > 8 x ULN |
| GGT | 1.1 - <2.0 x ULN | 2.0 – <3.0 x ULN | 3.0 – 8.0 x ULN | > 8 x ULN |
| Pancreatic Amylase | 1.1-1.4 x ULN | 1.5-1.9 x ULN | 2.0-3.0 x ULN | >3.0 x ULN |
| Uric Acid | 7.5-9.9mg/dL | 10-12.4 mg/dL | 12.5-15.0 mg/dL | >15.0 mg/dL |
| **CPK See Neuromuscular Toxicity** | | | | |
| **GASTROINTESTINAL** | | | | |
| Appetite | ---------- | Decreased appetite | Appetite very decreased, no solid food taken | No solid or liquid taken |
| Abdominal Pain | Mild | Moderate- No Treatment Needed | Moderate- Treatment Needed | Severe- Hospitalized for treatment |
| Diarrhea | Slight change in consistency and/or frequency of stools | Liquid stools | Liquid stools greater that 4x the amount or number normal for this child | Liquid stools greater than 8x the amount or number normal for this child |

| **GASTROINTESTINAL (continued)** | | | | |
|---|---|---|---|---|
| | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| Constipation | Slight change in the consistency/frequency of stool | Hard, dry stools with a change in frequency | Abdominal pain | Distention and Vomiting |
| Nausea | Mild | Moderate-Decreased oral intake | Severe-Little oral intake | Unable to ingest food or fluid for more than 24 hours |
| Vomiting | 1 episode/ day | 2-3 episodes per day | 4-6 episodes per day | Greater than 6 episodes per day or Intractable Vomiting |
| **ELECTROLYTES** | | | | |
| | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| Creatinine | 0.7-1.0 x ULN | 1.1-1.6 x ULN | 1.7-2.0 x ULN | >2.0 x ULN |
| Hypernatremia | | <145-149 mEq/L | 150-155 mEq/L | >155 mEq/L or abnormal sodium AND mental status changes |
| Hyponatremia | | 130-135 mEq/L | 129-124 mEq/L | <124 mEq/L or abnormal sodium AND mental status changes |
| Hyperkalemia | 5.0-5.9 mEq/L | 6.0-6.4 mEq/L | 6.5-7.0 mEq/L | >7.0 mEq/L or abnormal potassium AND cardiac arrhythamia |
| Hypokalemia | 3.0-3-5 mEq/L | 2.5-2.9 mEq/L | 2.0-2.4 mEq/L | <2.0 mEq/L or abnormal potassium AND cardiac arrhythmia |
| Hypercalcemia | 10.5-11.2mg/dL | 11.3-11.9 mg/dL | 12.0-12.9 mg/dL | >13.0 mg/dL |
| Hypocalcemia | 7.8-8.4 mg/dL | 7.0-7.7 mg/dL | 6.0-6.9 mg/dL | <6.0 mg/dL |

| ELECTROLYTES (Continued) | | | | |
|---|---|---|---|---|
| | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| Hypomagnesemia | 1.2-1.4 mEq/L | 0.9-1.1 mEq/L | 0.6-0.8 mEq/L | <0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia |
| Hypoglycemia | 55-65 mg/dL | 40-54 mg/dL | 30-39 mg/dL | <30 mg/dL or abnormal glucose AND mental status changes |
| Hyperglycemia | 116-159 mg/dL | 160-249 mg/dL | 250-400 mg/dL | >400 mg/dL or ketoacidosis |
| Proteinuria | Tr-1+ or <150 mg/day | 2+ or 150-499 mg/day | 3+ or 500-1000 mg/day | 4+ or Nephrotic syndrome >1000 mg/day |
| Hematuria | Microscopic <25 cells/hpf | Microscopic >25 cells/hpf | | Gross hematuria |
| **CENTRAL NERVOUS SYSTEM (CNS)** | | | | |
| Generalized CNS Symptoms | | | Dizziness | Hypotonic, hyporesponsive episodes; Seizures; Apnea/Bradycardia; Inconsolable crying > 3 hrs; |
| Headache | Mild | Moderate, Responds to non-narcotic analgesia | Moderate to Severe, Responds to narcotic analgesia | Intractable |
| Level of Activity | | Slightly irritable OR slightly subdued | Very irritable OR Lethargic | Inconsolable OR Obtunded |

| CENTRAL NERVOUS SYSTEM (CNS) (Continued) | | | | |
|---|---|---|---|---|
| | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| Visual | | Blurriness, diplopia, or horizontal nystagmus of < 1 hour duration, with spontaneous resolution | More than 1 episode of Grade 2 symptoms per week, or an episode of Grade 2 symptoms lasting more than 1 hour with spontaneous resolution by 4 hours or vertical nystagmus | Decrease in visual acuity, visual field deficit, or oculogyric crisis |
| Myelopathy | | None | None | Myelopathic/spinal cord symptoms, such as: pyramidal tract weakness and disinhibition, sensory level, loss of proprioception, bladder/bowel dysfunction |
| **PERIPHERAL NERVOUS SYSTEM** | | | | |
| Neuropathy/ Lower Motor Neuropathy | | Mild transient Paresthesia only | Persistent or progressive paresthesias, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss | Onset of significant weakness, decrease or loss of DTRs, sensory loss in "stocking glove" distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness. |
| Myopathy or Neuromuscu-lar Junction Impairment | Normal or mild (<2 x ULN) CPK elevation | Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation (<2 x ULN) | Proximal muscle weakness and/or atrophy affecting motor function +/- CPK elevation; or severe myalgias with CPK >2 x ULN; | Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms |

| OTHER | | | | |
|---|---|---|---|---|
| | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| Allergy | Pruritus without Rash | Pruritic Rash | Mild Urticaria | Severe Urticaria Anaphylaxis, Angioedema |
| Drug Fever (Rectal) | | 38.5-40C 101.3 – 104.0F | Greater than 40.0C Greater than 104.0F | Sustained Fever: Equal or greater than 40C (104.0F) for longer than 5 days |
| Cutaneous | Localized rash | Diffuse maculopapular Rash | Generalized urticaria | Stevens-Johnson Syndrome or Erythema multiforme |
| Stomatitis | Mild discomfort | Painful, difficulty swallowing, but able to eat and drink | Painful: unable to swallow solids | Painful: unable to swallow liquids; requires IV fluids |
| Clinical symptoms *not otherwise specified* in this table | No therapy; monitor condition | May require minimal intervention and monitoring | Requires medical care and possible hospitalization | Requires active medical intervention, hospitalization, or hospice care |
| Laboratory values *not otherwise specified* in this table | Abnormal, but requiring no immediate intervention; follow | Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug | Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug | Life-threatening severity; Requires immediate evaluation, treatment, and usually hospitalization; Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism that study drug |

## APPENDIX G: DECLARATION OF HELSINKI

# WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
## Ethical Principles for Medical Research Involving Human Subjects

*Adopted by the 18th WMA General Assembly, Helsinki, Finland, July 21964, and amended by the:*
*29th WMA General Assembly, Tokyo, Japan, October 1975*
*35th WMA General Assembly, Venice, Italy, October 1983*
*41st WMA General Assembly, Hong Kong, September 1989*
*48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996*
*52nd WMA General Assembly, Edinburgh, Scotland, October 2000*
*53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)*
*55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)*
*59th WMA General Assembly, Seoul, October 2008*

### A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

## B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent/assent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent/assent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent/assent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent/assent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent/assent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent/assent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

## C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent/assent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

## APPENDIX H: Package Insert for OraVerse® (phentolamine mesylate) Injection

# 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 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 intraoral 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). (1.1)

### DOSING AND ADMINISTRATION

| Amount of Local Anesthetic Administered | Dose of OraVerse |
|---|---|
| ½ Cartridge | ½ Cartridge (0.2 mg) |
| 1 Cartridge | 1 Cartridge (0.4 mg) |
| 2 Cartridges | 2 Cartridges (0.8 mg) |

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)

### DOSAGE FORM AND STRENGTH

0.4 mg/1.7 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 intravenous 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% and > control) is injection-site pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Septodont at 1-888-888-1441 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)

Revised: April 2011

## FULL PRESCRIBING INFORMATION: CONTENTS*



*Sections or subsections omitted from the Full Prescribing Information are not listed*

## FULL PRESCRIBING INFORMATION

### 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 intraoral 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).

### 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:

| Amount of Local Anesthetic Administered | Dose of OraVerse (mg) | Dose of OraVerse (Cartridges) |
|---|---|---|
| ½ Cartridge | 0.2 | ½ |
| 1 Cartridge | 0.4 | 1 |
| 2 Cartridges | 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.

#### 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).

(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.)

### 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 parenteral administration of phentolamine. These events usually occurred in association with marked hypertensive 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

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 3% 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

| Adverse Event | OraVerse | | | | Control |
|---|---|---|---|---|---|
| | 0.2 mg (N = 152) | 0.4 mg (N = 264) | 0.8 mg (N = 57) | Total (N = 473) | Total (N = 258) |
| | N (%) | N (%) | N (%) | N (%) | N (%) |
| Patients with AEs | 35 (23) | 82 (29) | 20 (35) | 137 (29) | 96 (37) |
| Tachycardia | 0 (0) | 17 (6) | 2 (4) | 19 (5) | 20 (8) |
| Bradycardia | 0 (0) | 5 (2) | 2 (4) | 7 (2) | 1 (0.3) |
| Injection site pain | 5 (3) | 15 (5) | 2 (4) | 22 (5) | 14 (4) |
| Post procedural pain | 3 (4) | 17 (6) | 5 (10) | 25 (6) | 23 (9) |
| Headache | 0 (0) | 10 (4) | 3 (5) | 13 (3) | 14 (4) |

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.

#### 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 those receiving control, included diarrhea, facial swelling, increased blood pressure/hypertension, injection site reactions, jaw pain, oral pain, paresthesia, pruritus, tenderness, upper abdominal pain and vomiting. The majority of these adverse reactions were mild and resolved within 48 hours. The few reports of paresthesia 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 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.

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.

### 7. DRUG INTERACTIONS

There are no known drug interactions with OraVerse.

#### 7.1 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 concentration increased immediately after OraVerse intraoral 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 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.

#### 8.2 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 human benefits of breastfeeding.

# OraVerse®

**8.4 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 ages 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. *(see Dosage and Administration (2))*

**8.5 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.

## 10. OVERDOSAGE

No deaths due to acute poisoning with phentolamine have been reported.

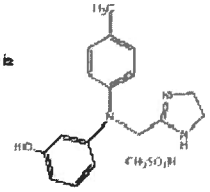
Overdosage with parenterally administered phentolamine is characterized chiefly by cardiovascular disturbances, such as arrhythmias, tachycardia, hypotension, and possibly shock. In addition, the following might occur: excitation, headache, sweating, pupillary contraction, visual disturbances, nausea,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

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

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

Phentolamine mesylate 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 formula is $C_{17}H_{19}N_3O \cdot CH_4O_3S$, and the chemical structure is:



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.

## 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 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 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 intraoral submucosal injection. The terminal elimination half-life of phentolamine in the blood was approximately 2-3 hours.

**Pediatrics**

Following OraVerse administration, the phentolamine $C_{max}$ 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) *(see Dosage and Administration section)*.

The pharmacokinetics of OraVerse in adults and in children who weighed more than 30 kg (66 lbs) are 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 (0.4mg) has not been studied in children.

## 13. NONCLINICAL TOXICOLOGY

**13.1 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-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. At doses up to 1950 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.

## 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 of local anesthetic effects on the teeth, mandible and maxilla has not been assessed.

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 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.

OraVerse 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 (62%). 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 OraVerse, 43% 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.

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

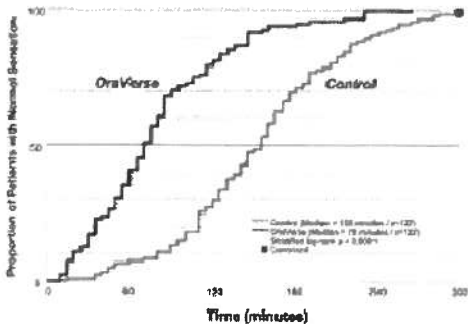
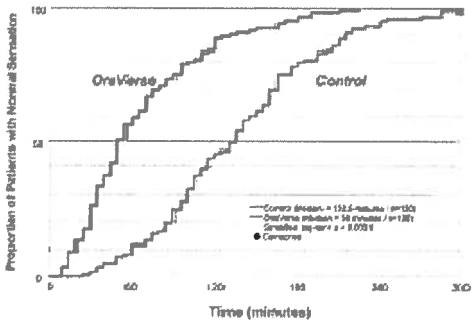



Figure 2: Kaplan-Meier Plot of Time to Recovery of Normal Sensation in the Upper Lip (ITT Analysis Data Set)




In Study 1 (mandibular), OraVerse accelerated: a) the recovery of the perception of normal appearance and function by 60 minutes (40%), b) the recovery of normal function by 60 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-blinded, 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 local anesthetic if they weighed 60.5 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 procedures, for mandibular and maxillary procedures combined, was reduced by 75 minutes (56%). Within 1 hour after administration of OraVerse, 414 patients (63%) reported normal lip sensation, while only 79 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

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.

NDC 0362-0101-50
NDC 0362-0101-10

Store at controlled room temperature, 20-25°C (68-77°F); 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

Novocol Pharmaceutical of Canada, Inc.
Cambridge, Ontario, Canada

for

Septodont, Inc
Lawrenceville, DE 19807

US Patent Nos.: 6,764,678; 6,872,380; 7,229,630
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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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Rev. 04/11 (2804-01)