Public Assessment Report

Decentralised Procedure

ORAUVERSE 400 MICROGRAMS/1.7 ML SOLUTION FOR INJECTION

UK/H/3713/001/DC
UK Licence No: PL 35061/0001

NOVALAR (UK) LIMITED
LAY SUMMARY

On 8th December 2011, the MHRA granted Novalar (UK) Limited a Marketing Authorisation (licence) for OraVerse 400 micrograms/1.7 ml solution for injection.

OraVerse 400 micrograms/1.7 ml solution for injection contains the active ingredient phentolamine mesilate.

OraVerse 400 micrograms/1.7 ml solution for injection is used to reverse the numbness in the lip and tongue caused by the injection of a local anaesthetic associated with a vasoconstrictor (of catecholamine type) given for a routine dental procedure such as teeth cleaning, scaling and planing, cavity filling, crowns.

OraVerse 400 micrograms/1.7 ml solution for injection works by increasing blood flow in the blood vessels at the injection site. This accelerates the return of normal sensation in the lip and tongue enabling you to speak, drink liquids and avoid drooling.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking OraVerse 400 micrograms/1.7 ml solution for injection outweigh the risks; hence this Marketing Authorisation was granted.
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 1: Information about initial procedure</td>
<td>4</td>
</tr>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>5</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflets</td>
<td>11</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>13</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>17</td>
</tr>
<tr>
<td>1 Introduction</td>
<td></td>
</tr>
<tr>
<td>2 Quality aspects</td>
<td></td>
</tr>
<tr>
<td>3 Non-clinical aspects</td>
<td></td>
</tr>
<tr>
<td>4 Clinical aspects</td>
<td></td>
</tr>
<tr>
<td>5 Overall conclusions</td>
<td></td>
</tr>
<tr>
<td>Module 6: Steps taken after initial procedure</td>
<td>72</td>
</tr>
</tbody>
</table>
## Module 1

<table>
<thead>
<tr>
<th>Product Name</th>
<th>OraVerse 400 micrograms/1.7 ml solution for injection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Hybrid application, Article 10(3)</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Phentolamine mesilate</td>
</tr>
<tr>
<td><strong>Pharmaceutical Form</strong></td>
<td>solution for injection</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>400 micrograms in 1.7 ml</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Novalar (UK) Limited</td>
</tr>
<tr>
<td></td>
<td>The Broadgate Tower, 20 Primrose Street</td>
</tr>
<tr>
<td></td>
<td>London</td>
</tr>
<tr>
<td></td>
<td>EC2A 2RS</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member State (CMS)</strong></td>
<td>Spain (ES), France (FR), Germany (DE) and Italy (IT)</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/3713/001/DC</td>
</tr>
<tr>
<td><strong>End of Procedure</strong></td>
<td>Final Position Day 60 of CMD (h) referral: 27th October 2011</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
OraVerse 400 micrograms/1.7 ml solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Phentolamine mesilate 400 micrograms in 1.7 ml (235 micrograms/ml).
Excipients:
Sodium 0.5 mg in 1.7 ml.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection.
Clear, colourless, isotonic, preservative free solution.
The pH of the solution ranges from 3.5 to 4.5.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Reversal of soft tissue anaesthesia (lip and tongue), and the associated functional deficits, resulting from an intraoral submucosal injection of a local anaesthetic containing a catecholamine vasoconstrictor, such as epinephrine, following a routine dental procedure such as teeth cleaning, scaling and planing, cavity filling, crowns (see section 5.1).

OraVerse is indicated in adults and children 6 years of age and older and weighing at least 15 kg.

4.2 Posology and method of administration
Posology
Adult patients
The recommended dose of OraVerse is based on the number of cartridges of local anaesthetic with vasoconstrictor administered:

<table>
<thead>
<tr>
<th>Amount of local anaesthetic administered [cartridge(s)]</th>
<th>Amount of OraVerse to be administered [cartridge(s)]</th>
<th>Dose of OraVerse (phentolamine mesilate) [micrograms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>½</td>
<td>½</td>
<td>200</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>400</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>800</td>
</tr>
</tbody>
</table>

The maximum recommended dose is 2 cartridges of OraVerse (800 micrograms of phentolamine mesilate).

Paediatric patients
As for adult patients, the recommended dose of OraVerse in paediatric patients is based on the number of cartridges of local anaesthetic with vasoconstrictor administered.

The maximum dose to be administered should be determined based on the age and weight of the patient, as follows:

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Maximum amount of OraVerse [cartridge(s)]</th>
<th>Maximum dose of OraVerse (phentolamine mesilate) [micrograms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11 years</td>
<td>15-30 kg</td>
<td>½</td>
<td>200</td>
</tr>
<tr>
<td>6-11 years</td>
<td>&gt; 30 kg</td>
<td>1</td>
<td>400</td>
</tr>
<tr>
<td>≥ 12 years</td>
<td>&gt; 30 kg</td>
<td>2</td>
<td>800</td>
</tr>
</tbody>
</table>
The efficacy of OraVerse in children less than 6 years of age has not yet been established. Currently available data are described in section 5.1 and 5.2 but no recommendation on a posology can be made.

Special populations

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

Patients with renal impairment:
OraVerse dose adjustment is not required in patients with renal impairment since phentolamine is metabolised principally in the liver, with less than 10% excreted unchanged in the urine.

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

Method of administration
For dental use.
OraVerse should be administered by intraoral submucosal injection following the dental procedure using the same location(s) and technique(s) (infiltration or block injection) employed for the administration of the local anaesthetic.
The OraVerse cartridge must be used in an appropriate syringe system that will permit aspiration before and during injection of solution. Each cartridge contains up to 0.2 ml overfill that allows aspiration prior to administration.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use
Patients should be instructed not to eat or drink until normal oral sensation returns.

Do not administer OraVerse if the product is discoloured or contains particulate matter.

Use of OraVerse is not recommended in patients undergoing complex dental procedures where post-procedural pain or haemorrhage is anticipated.
There are limited data on the use of OraVerse in patients at increased risk of bleeding, including patients treated with anticoagulants. Caution should be exercised when using OraVerse in such patients due to the increased risk of injection site haemorrhage.
To minimize the likelihood of intravascular injection, aspiration should be performed before OraVerse is injected. If blood is aspirated, the needle must be repositioned until no return of blood can be elicited by aspiration.

Following the intravenous or intramuscular administration of phentolamine mesilate at doses higher than recommended for reversal of soft tissue anaesthesia, myocardial infarction, cerebrovascular spasm, and cerebrovascular occlusion, usually in association with marked hypotensive episodes, have been reported.
As hypotension, tachycardia and cardiac arrhythmias may occur with the use of phentolamine and other alpha-adrenergic blocking agents, clinicians should be alert to the signs and symptoms of these events. OraVerse is not recommended in patients with severe or uncontrolled cardiovascular disease.

4.5 Interaction with other medicinal products and other forms of interaction
There are no known clinical drug interactions with OraVerse.

When OraVerse was administered as an intraoral submucosal injection 30 minutes after injection of a local anaesthetic containing 2% lidocaine HCl with 1:100,000 epinephrine, the lidocaine plasma concentration increased immediately after OraVerse intraoral injection. Lidocaine AUC and Cmax values were not affected significantly by administration of OraVerse. OraVerse administration did not affect the pharmacokinetics of epinephrine.
4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of phentolamine mesilate in pregnant women. Despite the fact that this active substance did not reveal a teratogenic potential, animal studies are insufficient with respect to reproductive toxicity (see section 5.3). OraVerse is not recommended during pregnancy.

Breast-feeding
It is unknown whether phentolamine is excreted in human milk. The excretion of phentolamine in milk has not been studied in animals. A decision to discontinue breast-feeding temporarily in favour of a treatment with OraVerse should be made taking into account the benefit of breast-feeding to the child and the benefit of OraVerse therapy to the woman.

Fertility
The effect of OraVerse on human fertility is unknown.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile
In clinical trials, the most frequently reported adverse reactions with OraVerse were post procedural pain and injection site pain, occurring in 6.0% and 5.3% of patients, respectively. The majority of adverse reactions were mild and resolved within 24 hours.

List of adverse reactions
Adverse reactions, based on experience from 418 dental patients enrolled in clinical trials, are listed in the table below. Within the system organ classes, adverse reactions are listed under headings of frequency using the following categories: common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Paraesthesia</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachycardia, bradycardia</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension/blood pressure increased</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Oral pain</td>
<td>Abdominal pain upper, diarrhoea, vomiting</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Pruritus, swelling face</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>Pain in jaw</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site pain</td>
<td>Injection site reaction, tenderness</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Post procedural pain</td>
<td></td>
</tr>
</tbody>
</table>

The few reports of paraesthesia were mild and transient and resolved during the 48-hour observation period.
Paediatric population
In 154 dental patients 3 to 17 years of age, common (≥1/100 to <1/10) adverse reactions consisted of tachycardia, bradycardia, blood pressure increased, and oral pain.

4.9 Overdose
Overdosage with parenterally administered phentolamine mesilate is characterised chiefly by cardiovascular disturbances such as arterial hypotension, reflex tachycardia, cardiac stimulation, arrhythmia, increase of systemic venous capacity, and possibly shock. These effects may be accompanied by headache, hyperexcitability and disturbances of vision, sweating, increased gastric motility, vomiting and diarrhoea, hypoglycaemia.

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.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Imidazoline derivatives, ATC code V03AB36.

Mechanism of action
Phentolamine is a competitive non-selective α1 and α2-adrenergic receptor blocker of relatively short duration. When applied to vascular smooth muscle, it produces an α-adrenergic block resulting in vasodilatation. However, the mechanism by which OraVerse accelerates reversal of soft-tissue anaesthesia and the associated functional deficits is not fully understood. 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. Phentolamine is not an antidote to local anaesthetics.

Clinical efficacy and safety
The safety and efficacy of OraVerse were evaluated in double-blinded, randomised, multicentre, controlled studies in patients undergoing dental restorative or periodontal maintenance procedures. In these studies, 484 patients were randomised to local anesthetic/vasoconstrictor combinations based on a 6:1:1:1 allocation ratio (lidocaine/epinephrine 1:100,000 (66%), articaine/epinephrine 1:100,000 (11%), prilocaine/epinephrine 1:200,000 (11%), and mepivacaine/levonordefrin 1:20,000 (11%)) prior to the dental procedure. The primary endpoint was time to normal lip sensation as measured by patient reported responses to lip palpation. The control group consisted of patients receiving a sham injection.

OraVerse reduced the median time to recovery of normal sensation in the lower lip by 85 minutes (55%) compared to control (p < 0.0001). The median time to recovery of normal lip sensation in the upper lip was reduced by 83 minutes (62%) compared to control (p < 0.0001). Within 1 hour after administration of OraVerse, 41% of patients reported normal lower lip sensation as compared to 7% in the control group, and 59% of patients in the OraVerse group reported normal upper lip sensation as compared to 12% in the control group. There was a significant reduction (p < 0.0001) in the time to return to normal oral function (speaking, smiling, drinking, and lack of drooling) and to normal perception in the OraVerse group compared to control.

The potential benefit of OraVerse concerning the reduction of self-inflicted injuries has not been studied during the clinical trials. Before administering OraVerse, the majority of patients included in the clinical studies were treated with a local anaesthetic and a vasoconstrictor (eg. epinephrine) at 1:100000 concentration. Limited data have been submitted to support the efficacy of OraVerse when a local anaesthetic and a vasoconstrictor (eg. epinephrine) at concentration less than 1:100000 is administered.

Paediatric population
In clinical studies, paediatric patients between the ages of 3 and 17 years received OraVerse. The safety, but not the efficacy, of OraVerse has been evaluated in patients 3 to 5 years of age. The median time to normal lip sensation in patients 6 to 11 years of age was reduced by 75 minutes (56%) compared to control (p < 0.0001). Within 1 hour after administration of OraVerse, 44 patients (61%) reported normal lip sensation, while only 9 patients (21%) in the control group reported normal lip sensation.
Elderly patients:
In clinical studies of OraVerse, 55 patients were 65 years of age and over, while 21 patients were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients.

5.2 Pharmacokinetic properties
Following OraVerse administration, phentolamine is 100% available from the submucosal intraoral injection site and peak concentrations are achieved 10 to 20 minutes after injection. Phentolamine systemic exposure increased linearly after 800 micrograms compared to 400 micrograms OraVerse intraoral submucosal injection. The terminal elimination half-life of phentolamine in the blood was approximately 2 to 3 hours.

Paediatric population:
Following OraVerse administration, the phentolamine Cmax was higher in children who weighed between 15 and 30 kg than in children who weighed more than 30 kg. However, phentolamine AUC was similar between the two groups. It is recommended that in children weighing 15 to 30 kg, the maximum dose of OraVerse should be limited to ½ cartridge (200 micrograms) (see section 4.2).

The pharmacokinetics of OraVerse in adults and in children who weighed more than 30 kg are similar after intraoral submucosal injection.

OraVerse has not been studied in children under 3 years of age or weighing less than 15 kg. The pharmacokinetics of OraVerse after administration of more than 1 cartridge (400 micrograms) has not been studied in children.

5.3 Preclinical safety data
According to the experimental data available, phentolamine did not reveal either a mutagenic or a teratogenic potential. Carcinogenicity studies with OraVerse have not been conducted. At doses up to 150 mg/kg (143 times human therapeutic exposure levels at the Cmax), phentolamine mesilate was shown to have no adverse effects on male fertility in the rat.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Mannitol (E 421)
Disodium edetate
Sodium acetate trihydrate (E 262i)
Acetic acid (E 260) (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 25°C.
Do not refrigerate or freeze.
Store in the original carton in order to protect from light.

6.5 Nature and contents of container
1.7 ml solution in a glass cartridge (type 1 colourless glass) with a standard plunger (bromobutyl rubber) and a blue flanged cap (aluminium) with a stopper (bromobutyl rubber).
Pack-sizes of 10 or 50 cartridges. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Novalar (UK) Limited
The Broadgate Tower, 20 Primrose Street
<table>
<thead>
<tr>
<th></th>
<th><strong>MARKETING AUTHORISATION NUMBER(S)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>PL 35061/0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th><strong>DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>08/12/2011</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th><strong>DATE OF REVISION OF THE TEXT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>08/12/2011</td>
</tr>
</tbody>
</table>
Module 3  
Patient Information Leaflet

Read all of this leaflet carefully before being given this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your dentist or doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your dentist or doctor.

In this leaflet:
1. What OraVerse is and what it is used for
2. Before you are given OraVerse
3. How to use OraVerse
4. Possible side effects
5. How to store OraVerse
6. Further information

1. WHAT ORAVERSE IS AND WHAT IT IS USED FOR
OraVerse contains a medicine called phenolamine mesilate.
OraVerse is used to reverse the numbness in the lip and tongue caused by the injection of a local anaesthetic associated with a vasoconstrictor (of catecholamine type) given for a routine dental procedure such as teeth cleaning, scaling and planing, cavity filling, crowns.
OraVerse increases blood flow in the blood vessels at the injection site. This accelerates the return of normal sensation in the lip and tongue enabling you to speak, drink liquids and avoid drooling.
OraVerse is for use in adults and in children 6 years of age and older and weighing at least 15 kg.

2. BEFORE YOU ARE GIVEN ORAVERSE
You should not be given OraVerse
- If you are allergic (hypersensitive) to phenolamine mesilate or any of the other ingredients of OraVerse listed in Section 6 below.

Make sure you tell your dentist or doctor before being given OraVerse
- If you have, or if you have ever had any heart conditions.
- If you are at increased risk of bleeding.
- If you have any liver problems.
Notify your dentist or doctor immediately if you feel dizzy or have palpitations right after OraVerse injection.
Contact your dentist or doctor immediately if you experience important oral bleeding after the dental procedure.

Children
OraVerse is not recommended for use in children under 6 years of age or weighing less than 15 kg.

Using other medicines
OraVerse is not known to affect, or be affected by any other medicines.
Please tell your dentist or doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
In particular, tell your dentist or doctor if you are taking anticoagulant medicines.

Using OraVerse with food and drink
Patients are advised not to eat or drink until oral feeding returns to normal.

Pregnancy and breast-feeding
Before you are given this medicine, tell your dentist or doctor if you are pregnant, planning to get pregnant, or if you are breast-feeding. OraVerse is not recommended during pregnancy. OraVerse should not be used during breast-feeding unless clearly necessary.

Driving and using machines
Your dentist or doctor will advise you when it is safe to drive and/or use machines.

Important information about some of the ingredients of OraVerse
This medicine contains less than 1 mmol sodium (23 mg) per cartridge, i.e. is essentially "sodium-free".

3. HOW TO USE ORAVERSE
OraVerse should only be given to you by a dentist or doctor. It will be given to you at the end of the dental procedure, when the numbing effect of the anaesthesia is no longer needed. It is injected in the mouth at the same location(s) and using the same technique(s) used for the injection of the local anaesthetic.

Use in adults
The recommended dose of OraVerse is based on a 1:1 ratio to the number of cartridges of local anaesthetic administered:

<table>
<thead>
<tr>
<th>Amount of Local Anaesthetic Administered</th>
<th>Amount of OraVerse</th>
</tr>
</thead>
<tbody>
<tr>
<td>½ Cartridge</td>
<td>½ Cartridge</td>
</tr>
<tr>
<td>1 Cartridge</td>
<td>1 Cartridge</td>
</tr>
<tr>
<td>2 Cartridges</td>
<td>2 Cartridges</td>
</tr>
</tbody>
</table>

The maximum dose is 2 cartridges of OraVerse.

Use in children
OraVerse is not recommended for use in children under 6 years of age or weighing less than 15 kg.
As for adult patients, the recommended dose of OraVerse in children is based on a 1:1 ratio to the number of cartridges of local anaesthetic administered.
The maximum dose to be administered depends on the age and weight of the children:

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Maximum amount of OraVerse</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11 years</td>
<td>15-30 kg</td>
<td>½ Cartridge</td>
</tr>
<tr>
<td>6-11 years</td>
<td>&gt; 30 kg</td>
<td>1 Cartridge</td>
</tr>
<tr>
<td>≥ 12 years</td>
<td>&gt; 30 kg</td>
<td>2 Cartridges</td>
</tr>
</tbody>
</table>
Use in the elderly
Use of OraVerse for elderly persons is not expected to be differ-
ent when compared to use for adults less than 65 years of age.

If you receive more OraVerse than you should
Your dentist or doctor will carefully calculate how much OraVerse
you should receive. It is unlikely that you will receive more Ora-
Verse than you should. If this happens, your dentist or doctor will
monitor and treat symptoms accordingly.
Signs of receiving too much OraVerse include: lowered blood
pressure, abnormal heart rate, headache, being overly excited,
eyesight problems, sweating, diarrhoea, vomiting and low blood
sugar.
If you have any further questions on the use of this product, ask
your dentist or doctor.

4. POSSIBLE SIDE EFFECTS
Like all medicines, OraVerse can cause side effects, although not
everybody gets them.
Common side effects (affects less than 1 person in 10)
• Pain at the location of injection.
• Pain at the location of the dental procedure.
• Oral pain.
• Slow heart rate.
• Increased heart rate.
• Headache.
• High blood pressure.

Uncommon side effects (affects less than 1 person in 100)
• Unusual or decreased sensations such as numbness, tingling,
prickling, burning in the mouth area (paraesthesia).
• Abdominal pain, diarrhoea, being sick (vomiting).
• Pain in jaw.
• Swelling of the face.
• Itching.
• Injection site reaction, tenderness.

If any of the side effects gets serious, or if you notice any side ef-
teffects not listed in this leaflet, please tell your dentist or doctor.

5. HOW TO STORE ORAVERSE
keep out of the reach and sight of children.
Do not use OraVerse after the expiry date which is stated on the
carton and the cartridge after EXP. The expiry date refers to the
last day of that month.

Do not store above 25 ºC.
Do not refrigerate or freeze.
Store in the original carton in order to protect from light.
This medicine must not be given to you if it is discoloured or if
there are particles in it.
Medicines should not be disposed of via wastewater or house-
hold waste. Your dentist or doctor is responsible for disposing of
any unused OraVerse correctly.

6. FURTHER INFORMATION
What OraVerse contains
– The active substance is phentolamine mesilate. 1.7 ml of
solution contains 400 micrograms phentolamine mesilate (235
micrograms/ml).
– The other ingredients are mannitol (E421), disodium edetate,
sodium acetate trihydrate (E262), acetic acid (E260) or sodium
hydroxide (for pH adjustment) and water for injections.

What OraVerse looks like and contents of the pack
The solution for injection should be clear and colourless.
OraVerse comes in a glass cartridge, in pack-sizes of 10 or
50 cartridges.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Novalar (UK) Limited
The Broadgate Tower, 20 Primrose Street
London EC2A 2RS
United Kingdom
Manufacturer:
Sanofi Winthrop Industrie
1, rue de la Vierge
Ambares et Lagrave
F- 33565 Carbon Blanc Cedex
France

This medicinal product is authorised in the Member States
of the EEA under the following names:
United Kingdom, Germany, France, Spain: OraVerse
Italy: Oraverse

This leaflet was last approved in 11/2011.
Module 4
Labelling

PAR OraVerse 400 micrograms/1.7 ml solution for injection

Phentolamine mesilate
Dental use

BN
EXP

11 mm
OraVerse®

One cartridge (1.7 ml) contains 400 micrograms phenolamine mesilate (235 micrograms/ml)

Excipients:
Mannitol (E421), disodium edetate, sodium acetate trihydrate (E260), acetic acid (E260) or sodium hydroxide (for pH adjustment), water for injections

Cartridges contain an overfill of up to 0.2 ml.

Do not store above 25 °C. Do not refrigerate or freeze.
Store in the original carton in order to protect from light.
Use only clear and colourless solution.
Keep out of the reach and sight of children.
Read the package leaflet before use.

OraVerse® 400 micrograms/1.7 ml solution for injection

10 cartridges of 1.7 ml

OraVerse® 400 micrograms/1.7 ml solution for injection

Phentolamine mesilate

Dental use
Solution for injection

10 cartridges of 1.7 ml with a standard plunger
**PAR OraVerse 400 micrograms/1.7 ml solution for injection**

**OraVerse**

**400 micrograms/1.7 ml solution for injection**

Phentolamine mesilate

**50 cartridges of 1.7 ml**

Dental use

Solution for injection

**50 cartridges of 1.7 ml with a standard plunger**

**OraVerse**

**400 micrograms/1.7 ml solution for injection**

Phentolamine mesilate

**50 cartridges of 1.7 ml**

OraVerse®

One cartridge (1.7 ml) contains 400 micrograms

Phentolamine mesilate (235 micrograms/ml)

Excipients:

Mannitol [E421], disodium edetate, sodium acetate

Bisulphite ([E262]), acetic acid ([E260]) or sodium

Hydroxide (for pH adjustment), water for injections

Cartridges contain an overfill of up to 0.2 ml

Do not store above 25 °C. Do not refrigerate or freeze.

Store in the original carton in order to protect from light.

Use only clear and colourless solution.

Keep out of the reach and sight of children.

Read the package leaflet before use.

Reserved for

Blue Box Information

Novilar (UK) Limited

The Broadgate Tower,

20 Prinmore Street,

London W1A 2RS

UK

PL 3306170001

UK/H/3713/001/DC
PAR OraVerse 400 micrograms/1.7 ml solution for injection

Phentolamine mesilate

Novalar (UK) Limited

Do not store above 25 °C. Do not refrigerate or freeze. Store in the original carton in order to protect from light.

Use only clear and colourless solutions.
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the UK (RMS) and CMS considered that the application for OraVerse 400 micrograms/1.7 ml solution for injection could be approved. This prescription only medicine (POM) is indicated in adults and children of 6 years of age and older and weighing at least 15 kg. This medicine is indicated for the reversal of soft tissue anaesthesia (lip and tongue), and the associated functional deficits, resulting from an intraoral submucosal injection of a local anaesthetic containing a catecholamine vasoconstrictor, such as epinephrine, following a routine dental procedure such as teeth cleaning, scaling and planing, cavity filling, crowns.

This application for OraVerse 400 micrograms/1.7 ml solution for injection is submitted as an abridged application according to Article 10(3) of Directive 2001/83/EC, as amended, claiming to be a hybrid medicinal product to Rogitine® ampoules 10 mg, solution for injection, first authorised in the UK to Ciba-Geigy PLC on 21st November 1989 (PL 00008/5070R). This licence has since undergone two changes of ownership to Novartis Pharmaceuticals UK Limited on 19th December 1997 (PL 00101/0540) and Alliance Pharmaceuticals Limited on 25th June 1998 (PL 16853/0012).

Phentolamine is a competitive non-selective α1 and α2-adrenergic receptor blocker of relatively short duration. When applied to vascular smooth muscle, it produces an α-adrenergic block resulting in vasodilatation. It probably accelerates recovery from soft tissue anaesthesia by increasing the blood flow to the local tissue and enhancing the clearance of the local anaesthetic from the tissue.

The product contains phentolamine mesilate, a widely-used, well-known active substance. However, since this application concerns a new indication and a new route of administration, the non-clinical review of literature is supplemented by a series of specific non-clinical studies (two pharmacology studies and several toxicology studies).

Nine clinical studies have been performed to support the application, two pharmacokinetic studies, three dose ranging studies and four pharmacodynamic studies.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory Risk Management Plan was provided for this product. It concluded that as phentolamine mesilate is a widely-used, well-known active substance that has been in clinical use for many years, routine pharmacovigilance is sufficient to monitor its safety profile. However, the MAH have made a commitment to:

- Monitor and study its use in the paediatric context.
- Study off-label use in a drug utilisation study.
- Study local reactions, cardiovascular events and reversal of soft tissue anaesthesia in treated patients in a PASS study.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>OraVerse 400 micrograms/1.7 ml solution for injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Phentolamine mesilate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Imidazoline derivatives V03AB36</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>400 micrograms/1.7 ml solution for injection</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/3713/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom (UK)</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Spain (ES), France (FR), Germany (DE) and Italy (IT)</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 35061/0001</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Novalar (UK) Limited The Broadgate Tower, 20 Primrose Street London EC2A 2RS United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Phentolamine mesilate
Chemical name: 3-[N-(2-Imidazolin-2-ylmethyl)-p-toluidino]phenol methanesulfonate

\[
\text{Phenol,3-[[\{(4,5\text{-dihydro-1H-imidazol-2-yl}methyl)-(4\text{-methylphenyl)}amino\}]-, methanesulfonate (salt)}
\]

3-[[\{(4,5\text{-dihydro-1H-imidazol-2-yl}methyl)-(4-methylphenyl)}amino]phenol methanesulphonate

Structural formula:

![Structural formula](image)

Molecular formula: \(C_{18}H_{23}N_{3}O_{4}S\)
Molecular weight: 377.5 g/mol

Appearance: A white or almost white, crystalline powder, which is slightly hygroscopic
Solubility: Soluble in water and in alcohol, slightly soluble in chloroform and practically insoluble in methylene chloride

Phentolamine mesilate is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the drug substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines.

Stability studies have been performed with the drug substance and no significant changes of the quality parameters were observed. On the basis of the results, the RMS agreed that a suitable re-test period could be approved.

P. Medicinal Product

Other Ingredients
Other ingredients consist of pharmaceutical excipients mannitol (E 421), disodium edentate, sodium acetate trihydrate (E 262i), acetic acid (E 260) (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections. All excipients comply with their relevant European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the development programme was to produce a solution for injection containing phentolamine mesilate that could be considered a hybrid medicinal product of Rogitine® ampoules 10 mg, solution for injection.

The applicant has provided suitable product development information. Valid justifications for the use and amounts of each excipient have been provided.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Satisfactory process validation data on batches have been provided. The applicant has committed to perform process validation on future commercial-scale batches.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis for any working standards used have been provided.

Container-Closure System
This product is packaged in type I colourless glass cartridges containing 1.7 ml of solution with a standard plunger (bromobutyl rubber) and a blue flanged cap (aluminium) with a stopper (bromobutyl rubber). The product comes in pack sizes of 10 or 50 cartridges.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation.

Stability of the product
Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a
shelf-life of 3 years with the storage instructions ‘Do not store above 25°C. Do not refrigerate or freeze. Store in the original carton in order to protect from light.’ This is satisfactory.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are pharmaceutically acceptable.

User testing results have been submitted for the PIL. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

**MAA Form**
The MAA form is pharmaceutically satisfactory.

**Quality Overall Summary**
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
It is recommended that a Marketing Authorisation is granted for this application from a quality point of view.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of phentolamine mesilate are well-known. However, since this application concerns a new indication and a new route of administration, the applicant has provided a review of the literature supplemented with a series of specific non-clinical studies to support the application.

Two pharmacology studies were conducted. These were:
- a primary pharmacodynamics study in support of the proposed clinical indication; and
- a secondary pharmacology study on the binding affinity for various human receptors.

Several GLP-compliant toxicology studies were also conducted:
- single- and repeat-dose toxicity/local tolerance studies in beagle dogs via the intended clinical route of administration and including the to-be-marketed formulation;
- genotoxicity studies with the drug substance used in OraVerse; and
- qualification studies for two impurities.

Pharmacology

Study 1

The Effects of Intraoral Injections of 2% Lidocaine with 1:100,000 Epinephrine and Phentolamine Mesilate on Local Blood Flow in the Dog

To investigate the presumed mechanism of action, a study was conducted on the effects of single intraoral submucosal injections of 2% lidocaine with 1:100,000 epinephrine and OraVerse on local blood flow in gingival/submucosal tissue of beagle dogs. The study design is presented in the following table:

<table>
<thead>
<tr>
<th>Group Number</th>
<th>N</th>
<th>Lidocaine/Epinephrine Injection (mL)</th>
<th>NV-101 Injection (mL)</th>
<th>Vehicle Injection (mL)</th>
<th>Phentolamine Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>0.3</td>
<td>0.0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0.3</td>
<td>0.5</td>
<td>0.0</td>
<td>0.012</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>0.3</td>
<td>0.0</td>
<td>0.5</td>
<td>0</td>
</tr>
</tbody>
</table>

The injection of lidocaine/epinephrine decreased blood flow in the treated side of the oral cavity of all groups by 55% to 74% relative to the 10 minute baseline period. Blood flow in Group 1 (lidocaine/epinephrine only) did not recover to baseline levels during the remaining 30 minutes of the study. Additionally in Group 1, tissue near the injection site became blanched immediately after the anaesthetic/vasoconstrictor injection and remained blanched until the end of the study. Blood flow in Group 2 dogs increased after the administration of OraVerse to levels 50-250% greater than the baseline period and returned to near-baseline levels in the majority of dogs by the end of the post-treatment period. Blood flow in Group 3 dogs was not affected by the administration of the OraVerse vehicle, and, as was observed for the dogs in Group 1, recovery of blood flow to baseline levels was not observed in these animals. Blood flow in the untreated side of the oral cavity remained unaffected by injections of local anaesthetic/vasoconstrictor, OraVerse, and vehicle administered in the treated side.
Mean blood flow rates before and after lidocaine/epinephrine injection followed by no injection (Group 1), OraVerse injection (Group 2) or OraVerse vehicle injection (Group 3) are presented in Figure 1.

**Figure 1: Mean Blood Flow Before and After Lidocaine/Epinephrine Injection Followed by No Injection, NV-101, or NV-101 Vehicle**

It was concluded that OraVerse appeared to reverse the vasoconstrictive effect of epinephrine through $\alpha$-adrenergic receptor blockade and concentrations of phentolamine and lidocaine/epinephrine in the solutions administered in this study were comparable (based on body surface area) to the concentrations of these drugs used in clinical trials of OraVerse. It was concluded that the increase in blood flow induced by OraVerse could be expected to result in an increased rate of anaesthetic clearance from nearby nerves and thus accelerate the reversal of soft tissue anaesthesia and the associated functional deficits induced by the administration of anaesthetic/vasoconstrictor combinations.

**Study 2**

**General Side-Effect Profile Screening Program**

An *in vitro* study was conducted to assess the binding affinity of phentolamine and the OraVerse impurities N1-2[N-(3-hydroxyphenyl)-N-(4- toluyl)aminoacetyl]-ethylenediamine (HTAEDA) and phentolamide to 63 types of human receptors as part of a standard side-effect profile screen. Phentolamine had strong and equal binding affinities at $\alpha_1$- and $\alpha_2$-adrenergic receptors, but had no appreciable binding at the other 61 types of receptors tested. HTAEDA and phentolamide at $1 \times 10^{-5}$ and $1 \times 10^{-5}$ M did not bind any of the 63 receptor types in the assay, suggesting that they have a low potential for producing off-target effects through any of the receptors studied.
Pharmacology Conclusion
The results of the blood-flow investigations support the postulated clinical mechanism of action. Additional safety pharmacology studies are not required, as observations on the cardiac and respiratory systems were included in the single- and repeat-dose toxicology studies presented below.

Toxicology

Study 3

Local tolerance at the Intraoral Injection Site and Systemic Toxicity Study of Phentolamine Mesilate, HTAEDA, and Phentolamide in the Dog.

This study included evaluations of both local and systemic toxicity and also included dosing with the two primary impurities in OraVerse 400 micrograms/1.7 ml solution for injection (HTAEDA and phentolamide).

Five groups of 7 adult male beagle dogs were given an intraoral injection of one or more of the test article components, or the OraVerse vehicle, into the mandible and into the maxilla. Group 1 was given the OraVerse vehicle. Group 2 was given a test article consisting of phentolamine mesilate (0.024 mg/kg), HTAEDA (0.00054 mg/kg) and phentolamide HCl (0.0004 mg/kg). The total dose of phentolamine mesilate administered (0.024 mg/kg) was split evenly between the mandible (0.012 mg/kg) and the maxilla (0.012 mg/kg). Normalised for body surface area, the total dose of phentolamine mesilate administered to each dog was equivalent to the highest dose studied in clinical trials (0.8 mg) while the dose administered at either individual injection site was equivalent to the proposed standard clinical dose (0.4 mg) of OraVerse. Group 3 received these three test article components at ten times the total dose given to Group 2 (0.24 mg/kg phentolamine mesilate, 0.0054 mg/kg HTAEDA, 0.004 mg/kg phentolamide HCl). Group 4 was given phentolamine mesilate only (no HTAEDA or phentolamide HCl) at ten times the level of phentolamine mesilate given in Group 2 (0.24 mg/kg). Group 5 received injections of HTAEDA in combination with phentolamide HCl at ten times the level of the test articles given in Group 2 (0.0054 mg/kg HTAEDA, 0.004 mg/kg phentolamide HCl).

Analysis of the dosing solutions before and after dosing (up to 15 days post-dose) indicated that all concentrations were within 10% of the target.

There were no deaths. There were no test article-related effects on physical signs, heart rate, temperature, respiration, body weight, food consumption, haematology, blood chemistry, urinalysis, ophthalmology, gross necropsy, organ weights, or histopathology of a full panel of tissues as well as the oral tissues.

It was concluded that a single intraoral injection of phentolamine mesilate at doses up to 0.24 mg/kg (10 times the dog equivalent of the maximum recommended clinical dose, based on body surface area) was well tolerated in beagle dogs.

Study 4

Repeated-Dose Local Tolerance at the Intraoral Injection Site and Systemic Toxicity Study of Phentolamine Mesilate, HTAEDA, and Phentolamide in the Beagle Dog.
This study included evaluations of both local and systemic toxicity and also included dosing with two known impurities in the OraVerse drug product (HTAEDA and phentolamide). The treatment groups are listed in the following table:

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Dose (µg/kg)</th>
<th>Dosing Solution Concentration (µg/ml)</th>
<th>Total Number of Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control (Vehicle)</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Phentolamine mesylate</td>
<td>12</td>
<td>235</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>HTAEDA</td>
<td>0.27</td>
<td>5.25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phentolamide HCl</td>
<td>0.20</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Phentolamine mesylate</td>
<td>120</td>
<td>2350</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HTAEDA</td>
<td>2.7</td>
<td>52.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phentolamide HCl</td>
<td>2.0</td>
<td>39.0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Phentolamine mesylate</td>
<td>120</td>
<td>2350</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HTAEDA</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phentolamide HCl</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Phentolamine mesylate</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HTAEDA</td>
<td>2.7</td>
<td>52.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phentolamide HCl</td>
<td>2.0</td>
<td>39.0</td>
<td></td>
</tr>
</tbody>
</table>

Five groups of 3 adult male beagle dogs were given an intraoral injection of one or more of the test article components or the OraVerse vehicle into the mandible and into the maxilla on Days 1, 8 and 15. Group 1 was given the OraVerse vehicle. Group 2 was given a test article consisting of phentolamine mesylate (0.024 mg/kg), HTAEDA (0.00054 mg/kg) and phentolamide HCl (0.0004 mg/kg). The total dose of phentolamine mesylate administered (0.024 mg/kg) was split evenly between the mandible (0.012 mg/kg) and the maxilla (0.012 mg/kg). Normalised for body surface area, the total dose of phentolamine mesylate administered to each dog was equivalent to the highest dose studied in clinical trials (0.8 mg) while the dose administered at either individual injection site was equivalent to the proposed standard clinical dose (0.4 mg). Group 3 received the three test article components at ten times the total dose given to Group 2 (0.24 mg/kg phentolamine mesylate, 0.0054 mg/kg HTAEDA, 0.004 mg/kg phentolamide HCl). Group 4 was given phentolamine mesylate only (no HTAEDA or phentolamide HCl) at ten times the level of phentolamine mesylate given in Group 2 (0.24 mg/kg). Group 5 received injections of HTAEDA in combination with phentolamide HCl at ten times the level of these test articles given in Group 2 (0.0054 mg/kg HTAEDA, 0.004 mg/kg phentolamide HCl).

Analysis of the dosing solutions before dosing indicated that all concentrations were within 10% of the target. After dosing (up to 7 days), analysis of the dosing solutions indicated an increase in the concentration of phentolamide HCl in the dosing solutions for Groups 2, 3 and 5. The increase in phentolamide HCl (>10% of the target for Group 3) might be attributable to the rapid breakdown of phentolamine mesylate to phentolamide HCl.

There were no deaths. There were no test article-related effects on physical signs, heart rate, temperature, respiration, body weight, food consumption, haematology, blood chemistry, urinalysis, ophthalmology, gross necropsy, organ weights, or histopathology of a full panel of tissues as well as the oral tissues.
It was concluded that repeated intraoral injection of phentolamine mesilate at doses up to 0.24 mg/kg (10 times the dog equivalent of the maximum recommended clinical dose, based on body surface area) was well tolerated in beagle dogs.

**Toxicology Conclusion**
The duration of the toxicity studies with the proposed product and impurities is sufficient to support the application. There were no findings of toxicological concern in the single- or repeated-dose studies.

**Genotoxicity**

**Study 5**

**Bacterial Reverse Mutation Assay**

The study was conducted in *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 and in the *E. coli* tester strain WP2 *uvrA* in the presence and absence of metabolic activation with Aroclor-induced rat liver S9. Phentolamine mesilate was dissolved in sterile distilled water. The plate incorporation method was used.

Phentolamine mesilate was applied at concentrations of 50, 150, 500, 1500 or 5000 μg/plate. The vehicle and positive controls, and all dose levels of phentolamine mesilate were plated in triplicate in the presence and absence of Aroclor-induced rat liver S9 and cultured overnight. The effects of the test article were judged positive if the mean number of revertant colonies at the peak of the dose response was ≥ 2.0 times the vehicle control mean in strains TA98, TA100, and WP2 *uvrA*, and ≥ 3.0 times the vehicle control for the other strains.

No mutagenic response or precipitation of phentolamine was observed in any tester strain. No mutagenicity was found, no precipitation developed, and background lawn toxicity was evident only at 5000 μg/plate. The positive control substances demonstrated significant mutagenicity.

It was concluded that phentolamine mesilate was found to be non-mutagenic in the bacterial reverse mutation assay in the presence or absence of metabolic activation.

**Study 6**

**In-vitro Chromosome Aberration Test**

In an in-vitro chromosomal aberration study in Chinese hamster ovary cells, doses were chosen for the assay on the basis of a preliminary toxicity test and ranged from 12.5 to 300 μg/mL for both the non-activated and the S9-activated 4-hour exposure groups, and from 1.25 to 35 μg/mL for the non-activated 20-hour continuous exposure group. Numerical aberrations at the highest concentration evaluated (8.5% at 150 μg/mL) were slightly above the historical control range (0.0 to 6.5%) after a 4-hour exposure to phentolamine without metabolic activation. The observed increase was not statistically significant for dose-dependency and the concentration of 150 μg/mL was associated with substantial toxicity, viz. 54% cell growth inhibition, relative to the solvent control. Structural aberrations were slightly increased after a 4-hour exposure to phentolamine with metabolic activation only at the highest concentration evaluated (4.5% at 150 μg/mL), but remained within the historical control range (0.0 to 5.0%). The increase was therefore considered not biologically significant.
significant. Neither numerical nor structural aberrations were increased after a 20-hour exposure without metabolic activation.

It was concluded that phentolamine mesilate was negative for the induction of structural aberrations and equivocal for the induction of numerical aberrations in CHO cells in the non-activated test system.

**Study 7**

**Mammalian Erythrocyte Micronucleus Test**

Five mice/sex/dose were given single IP injections of phentolamine mesilate at doses of 25, 50 or 100 mg/kg, the saline vehicle, or the positive control cyclophosphamide (CP) which were investigated 24 hours after dosing. Five mice/sex treated with 100 mg/kg phentolamine mesilate and five mice/sex given the saline vehicle alone were investigated 48 hours after dosing. Two thousand erythrocytes from each mouse were scored in a blinded fashion for the presence or absence of micronuclei and for the percentage of polychromatic erythrocytes (PCE).

No significant increase in the incidence of micronucleated polychromatic erythrocytes was observed in any phentolamine-treated animals relative to the numbers seen in vehicle-treated control mice. The positive control substance increased the numbers of micronucleated cells in the expected manner.

It was concluded that phentolamine mesilate at the doses tested was non-toxic to bone marrow cells and negative for the induction of clastogenic effects in this assay.

**Genotoxic Conclusion**

The conduct of the genotoxicity cells was adequate. It is accepted that there were no findings indicative of a genotoxic response.

**Local Tolerance**

Local tolerance was assessed in the single- and repeated-dose studies described above. In the single-dose study, examination of the oral cavity was conducted to check for the appearance of tissues at the injection site, bleeding, and colour changes pre-dose, and at 10 minutes, 1, 3 and 24 hours, and 3, 8 and 15 days post-dose. Gingival/submucosal tissue surrounding the injection site of each quadrant was examined histopathologically for morphological changes visible with H&E staining. These tissue sections from the mandible contained the lingual and alveolar nerves and sections from the maxilla contained the infraorbital and superior alveolar nerves.

Minimal bleeding was observed at 10 minutes post-injection in some dogs in Groups 3, 4 and 5. Moderate bleeding was noted in one dog from Group 2 at 10 minutes. A haematoma was noted in one dog in Group 3 and one dog in Group 5 at the 10-minute, 1-hour and 3-hour post-injection examinations.

At necropsy, petechia and/or ecchymosis at the sites of injection were noted in all groups, including controls. Nerve fibre degeneration was found in one dog given the low doses of phentolamine, HTAEDA, and phentolamide HCl (Group 2). Degeneration was found in segments of branches of the superior alveolar nerve (maxilla), but not in the inferior alveolar
nerve (mandible) of this animal. There were no other inflammatory or degenerative lesions in surrounding tissues. The degenerative change in the superior alveolar nerve apparently resulted from placement of the needle or was present before the study and was not considered related to the test articles. Minimal superior alveolar nerve fibre degeneration was also observed in one control dog. Other microscopic changes were consistent with findings typically seen in dogs and were not considered related to treatment.

It was concluded that a single intraoral injection of phentolamine mesilate at doses up to 0.24 mg/kg (10 times the dog equivalent of the maximum recommended clinical dose, based on body surface area) was well tolerated at the intraoral injection site in beagle dogs.

In the repeated-dose study, the examinations were as described for the single-dose study and were conducted 24 hours after each dose (Days 1, 8 and 15 days post-dose). Observations were also made on Days 3, 4, 10, 11, 17, 18 and 22.

While the majority of the observations were deemed normal, there were some changes in the soft tissue appearance (haematoma, swelling and erythroplakia), colour (hyperaemic and cyanotic), and bleeding (minimal) at the injection sites. These observations typically occurred within three hours of dosing but had resolved by 24 hours after dosing without intervention. There were no changes in the nerves at the injection sites of dogs from any dose group that were considered directly related to the test articles. Nerve fibre degeneration of moderate severity was present in the inferior alveolar nerve near the injection site in one control dog. The nerve degeneration was apparently the result of needle trauma during injection and might have been associated with the inflammation at that site.

Chronic inflammation of minimal severity was also present in perineural tissues at the mandibular injection site adjacent to the inferior alveolar nerve in at least one animal in Groups 3, 4 and 5. Lymphohistiocytic or mixed inflammation was observed in subcutaneous tissues at the maxillary injection site in one dog from each of the five groups. The inflammation was always of minimal severity.

It was concluded that repeated intraoral injections of phentolamine mesilate at doses up to 0.24 mg/kg (10 times the dog equivalent of the maximum recommended clinical dose, based on body surface area) were well tolerated at the intraoral injection site in beagle dogs.

**Impurities**

HTAEDA and phentolamide are degradants of the phentolamine mesilate in OraVerse 400 micrograms/1.7 ml solution for injection.

At physiologically relevant concentrations, neither of the two degradants bound significantly to any of the 63 receptor types in a generalised binding assay (including α1- and α2-adrenergic receptors), suggesting that they have a low potential for producing effects through any of the receptor types studied.

The single- and repeated-dose toxicity studies used dosing solutions that contained the impurities at levels relative to phentolamine of 3% HTAEDA and 2% phentolamide in order to qualify them (see above). Single and multiple intraoral injections of HTAEDA at doses up to 0.0054 mg/kg and phentolamide HCl at doses up to 0.004 mg/kg were well tolerated in beagle dogs.
HTAEDA and phentolamide were also studied individually in GLP genotoxicity studies conducted on behalf of the Applicant.

Study 8

Bacterial Reverse Mutation Assay

HTAEDA was studied in a bacterial reverse mutation assay at dose levels of 1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 μg per plate. No precipitate was observed but toxicity was observed at 1500 and 5000 μg per plate. There was no evidence of mutagenicity.

Study 9

In-vitro Mammalian Chromosome Aberration Test

In an in-vitro chromosome aberration assay in Chinese hamster ovary cells, the doses of HTAEDA ranged from 25 to 250 μg/mL for both the non-activated and the S9-activated 4-hour exposure groups, and ranged from 6.25 to 150 μg/mL for the non-activated 20-hour continuous exposure group. The percentage of cells with structural or numerical aberrations in the test article-treated groups was not significantly increased above that of the solvent control at any dose level (p>0.05, Fisher's exact test). It was concluded that HTAEDA was negative for the induction of structural and numerical chromosome aberrations in CHO cells in both the non-activated and the S9-activated test systems.

Study 10

Bacterial Reverse Mutation Assay

Phentolamide was studied in a bacterial reverse mutation assay at dose levels of 50, 150, 500, 1500 and 5000 μg per plate. No precipitate was observed. No appreciable toxicity was observed except for reductions in revertant counts at 5000 μg per plate in some test conditions. There was no evidence of mutagenicity.

Study 11

In-vitro Mammalian Chromosome Aberration Test

In an in-vitro chromosome aberration assay in Chinese hamster ovary cells, the doses of phentolamide ranged from 75 to 850 μg/mL for both the non-activated 4- and 20-hour exposure groups, and ranged from 25 to 300 μg/mL for the S9-activated 4-hour exposure group. At the conclusion of the treatment period, the colour of the medium changed from red to rust or orange because of the presence of test article at dose levels ≥75 μg/mL in the non-activated 4- and 20-hour exposure groups, and at dose levels ≥200 μg/mL in the S9-activated 4-hour exposure group.

The percentage of cells with structural aberrations in the non-activated 4-hour exposure group was significantly increased above that of the solvent control at 300 μg/mL (p≤0.05, Fisher's exact test). The Cochran-Armitage test was negative for a dose response (p>0.05). However, the percentage of cells with structural aberrations in the test article-treated group (3.5%) was within the historical solvent control range of 0.0% to 5.0%. Therefore, it is not considered to be biologically significant. The percentage of cells with numerical aberrations in the test
The percentage of cells with structural aberrations in the S9-activated 4-hour exposure group was significantly increased above that of the solvent control at 100 µg/mL (p ≤ 0.01, Fisher's exact test). The Cochran-Armitage test was also positive for a dose response (p ≤ 0.05). However, the percentage of cells with structural aberrations in the test article-treated group (4.5%) was within the historical solvent control range of 0.0% to 5.0%. Therefore, it is not considered to be biologically significant. The percentage of cells with numerical aberrations in the test article-treated group was not significantly increased above that of the solvent control at any dose level (p > 0.05, Fisher's exact test).

The percentage of cells with structural aberrations in the non-activated 20-hour exposure group was significantly increased above that of the solvent control at 300 µg/mL (p ≤ 0.01, Fisher's exact test). The Cochran-Armitage test was also positive for a dose response (p ≤ 0.05). However, the percentage of cells with structural aberrations in the test article-treated group (6.0%) was only slightly outside the historical solvent control range of 0.0% to 5.0%. Therefore, it is not considered to be biologically significant. The percentage of cells with numerical aberrations in the test article-treated group was not significantly increased above that of the solvent control at any dose level (p > 0.05, Fisher's exact test).

It was concluded that phentolamide was negative for the induction of structural and numerical chromosome aberrations in CHO cells in both the non-activated and the S9-activated test systems. The Expert points out that, even though the findings in the chromosomal aberration test for phentolamide were not considered biologically significant, an in vivo study was conducted. The data show that the numbers of chromosome aberrations in the treated groups are not on par with nor of the same order of magnitude as those induced by the positive controls. The conclusion that the small increases seen in this study are not indicative of a clastogenic effect is accepted.

**Study 11**

**Mammalian Erythrocyte Micronucleus Test**

Phentolamide HCl was tested in the mouse micronucleus assay at doses of 100, 200 or 400 mg/kg. Reductions in the ratio of polychromatic erythrocytes to total erythrocytes (PCEs/ECs ratio) of up to 42% were observed in the male test article groups 24 hours post-dose. Reductions in the PCEs/ECs ratio of up to 11% were observed in the female test article groups relative to the vehicle control 24 hours post-dose. Even though not dose-dependent, these reductions suggest bone marrow exposure to the test article. No appreciable reductions in PCEs/ECs ratio were observed in the 48-hour test article-treated groups. No significant increase in the incidence of micronucleated polychromatic erythrocytes in test article-treated groups relative to the respective vehicle control groups was observed in male or female mice at 24 or 48 hours after dose administration (p > 0.05, Kastenbaum-Bowman Tables).

Because the concentration of the 400 mg/kg dosing solution (at 67% of nominal) did not meet the acceptance criteria, a repeat study was done at that dose and including negative and positive controls. The results were essentially similar to those described above.
It was concluded that a single intraperitoneal dose of phentolamide HCl at up to and including the maximum tolerated dose of 400 mg/kg did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in bone marrow of male and female ICR mice. Therefore, phentolamide HCl was concluded to be negative in the mouse micronucleus assay.

The negative effect in the in vivo micronucleus study provides reassurance that phentolamide is not clastogenic and supports the interpretation that the in vitro test was negative.

The series of genotoxicity studies conducted on the degradants provides evidence that they are neither mutagenic nor clastogenic and it is accepted that they have been adequately qualified.

The active substance and all the excipients are reported to comply with the European Pharmacopoeia. However, in the drug substance, it is possible for genotoxic alkyl mesilate esters to be present at levels below 1 ppm. It is reported that for these impurities, this level is as low as reasonably possible (ALARP) based on their limit of detection in the analytical assay. The combined maximum intake of the impurities is 1.6 ng at the maximum dose of phentolamine mesilate in the proposed indication (0.8 mg). This intake is a factor of 1000 below the Threshold of Toxicological Concern of 1.5 µg/day for chronically administered drugs (CPMP/SWP/5199/02 Guideline on the limits of genotoxic impurities, 2006). Taking into account the intended single-dose regimen, the genotoxic impurities are considered to present no safety risk in the context of the proposed indication.

Literature review
Where animal data were not available, human data have been presented. A thorough review of the relevant literature has been provided. Due to the extensive clinical experience with phentolamine, it will not be reproduced here except for the following brief reference to a relevant pharmacology paper.

The Pharmacology section of the literature reviewed includes reports that show that phentolamine reduced vasoconstriction in the oral cavity of cats and in tissues other than oral in dogs and pigs.

The non-clinical overview and summary have been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Environmental Risk Assessment

A Phase I Environmental Risk Assessment has been provided.

Bioaccumulation
The potential for bioaccumulation was calculated for phentolamine mesilate. This involved estimating the biodegradability of the substance in its non-ionised form, therefore the calculations performed in the case of phentolamine mesilate are considered to represent a worst-case scenario. The maximum value was calculated at being 3.36, which is below the trigger value of 4.5 as specified in the CHMP guideline. It was concluded that phentolamine mesilate has a low potential for bioaccumulation and therefore OraVerse 400 micrograms/1.7 ml solution for injection is unlikely to represent a risk for the environment following its prescribed usage.
**Toxicity**
It is reported that phentolamine has not been classified as dangerous for having any persistent bioaccumulative and toxic (PBT) potential in the European database ESIS (European chemical Substances Information System). The published toxicity data indicate that phentolamine is neither genotoxic, carcinogenic nor a reproductive toxicant. Phentolamine mesilate has been assessed for potential endocrine disrupting effects using the toxicology flow chart developed by ECETOC. It was concluded that there was no evidence for a potential for endocrine disruption.

**Predicted Environmental Concentration (PEC)**
The PEC was calculated and was found to be below the trigger value for a Phase II analysis. This is satisfactory.

Overall, the authors concluded that there was no evidence for PBT properties on the part of phentolamine mesilate.

It is recommended that a Marketing Authorisation is granted for this application from a non-clinical point of view.
III.3  CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

A total of nine studies were conducted according to GCP standards and have been provided in support this application.

Three dose-ranging studies were conducted in adult healthy subjects to establish the dose of phentolamine mesilate that accelerates the reversal of soft tissue anaesthesia.

Two pharmacokinetic (PK) studies: one in paediatric dental subjects and one in adult healthy subjects.

Pharmacodynamics (PD) were characterised in the two Phase III studies, a paediatric pharmacokinetic Phase II study and two other Phase II studies, one in children aged 3 to 11 years old and one in dental patients aged 10 to 61 years old.

Phase I/II Studies

Dose ranging studies

The rationale for selection of the dose of the test product was based on results from the three Phase I/II dose ranging studies. The test product used in these studies was a generic formulation of phentolamine mesilate, not the final product intended to be marketed. This generic formulation was presented in 2 ml vials as powder requiring reconstitution prior to IV or IM injection. The new product is presented in standard dental cartridges readily available for use by dentists without preliminary reconstitution.

Dose Ranging Study 1 – 0.2 mg dose

This study compared the time to the return of normal sensation in the lip in healthy volunteers after anaesthesia had been induced in the lip by administration of lidocaine with epinephrine in an inferior alveolar nerve block (IANB).

Twenty adult subjects were randomly assigned to receive a single injection of placebo (1.8 mL) or 0.2 mg of phentolamine mesilate (1.8 mL of a 0.11 mg/mL solution) at 60 minutes after administration of the IANB, in the same site where the anaesthetic was injected. All subjects self-evaluated the return of normal sensation in the lip, tongue, teeth, and chin by palpations at 5-minute intervals beginning 5 minutes before the phentolamine mesilate or placebo injection and continuing until all subjects present for testing had achieved the return of normal sensation in lip, tongue, teeth, and chin.

The results were as follows:
Phentolamine reduced the duration of soft-tissue anesthesia. Recovery in the lip, chin, and tongue was significantly faster in subjects in the phentolamine-treated group than in the placebo-treated group. No dose related adverse events were seen.

**Dose Ranging Study 2 – 0.02 mg, 0.06 mg and 0.4 mg**

This was a dose-ranging, single centre, double-blind, randomised, placebo-controlled study of the safety and efficacy of a single injection of phentolamine mesilate in the mandibular region of healthy subjects.

Forty healthy adult male and female (20 male, 20 female) subjects received a conventional inferior alveolar nerve block (IANB) using 1.8 mL of 2% lidocaine (36 mg) with 1:100,000 epinephrine (18 μg). This injection was placed in a standardized location by a licensed dentist to achieve a right- or left-side IANB. Subjects were randomly assigned to receive a single injection of placebo (1.8 mL), 0.02 mg of phentolamine mesilate (1.8 mL of a 0.011 mg/mL solution), 0.06 mg of phentolamine mesilate (1.8 mL of a 0.033 mg/mL solution), or 0.4 mg of phentolamine mesilate (1.8 mL of a 0.2267 mg/mL solution) at 60 minutes after administration of the IANB, in the same site where the anaesthetic was injected. Randomisation was 1:1:1:1, resulting in ten subjects per group. All subjects completed the trial.

All subjects were asked to rate sensation in the lips, tongue, teeth, and chin by self-palpation at 5 minutes before study drug injection (i.e., 55 minutes after anaesthetic), and at 5-minute intervals beginning 5 minutes after study drug injection until all subjects had achieved the return of normal sensation.

Sensation was assessed in the lip by pinching with 2 fingers (or thumb and forefinger), in tongue by pinching the lateral edge of the tongue while extruding the tongue outside the mouth, in the teeth by biting (bringing the teeth together) and moving the teeth from side to side when the teeth were brought together, and in the chin by pressing with the forefinger. Responses for the lip, tongue, and chin were recorded separately and categorised as 1) numb (no feeling), feeling of pins and needles (tingling), and 3) normal sensation. Responses for the teeth were recorded separately and categorised as numb (no feeling) and normal sensation.
The time to return to normal sensation was measured by counting the minutes from study drug injection to the first time the subject reported normal sensation in a tissue that had been anaesthetised. The primary efficacy endpoint was time to the return of normal sensation in the lips. Secondary endpoints were time to the return of normal sensation in the teeth, tongue, and chin.

The time to the return of normal sensation was analysed with the $t$-test for each tissue (lip, chin, tongue and teeth) to determine the significance of differences between the placebo and phentolamine-treated groups. Comparisons with a $p$ value of 0.05 or less were considered significantly different.

The primary results were as follows:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Statistical Parameter</th>
<th>Lip</th>
<th>Chin</th>
<th>Tongue</th>
<th>Teeth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>157.6</td>
<td>150.6</td>
<td>115.1</td>
<td>120.1</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>162.5</td>
<td>152.5</td>
<td>127.5</td>
<td>135.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>47.6</td>
<td>35.6</td>
<td>43.0</td>
<td>42.1</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>81-220</td>
<td>81-215</td>
<td>35-175</td>
<td>26-174</td>
</tr>
<tr>
<td>0.02 mg</td>
<td>N</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>104.6</td>
<td>89.0</td>
<td>79.0</td>
<td>84.4</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>100.0</td>
<td>96.0</td>
<td>86.5</td>
<td>93.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>27.0</td>
<td>22.1</td>
<td>30.8</td>
<td>37.1</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>70-160</td>
<td>46-120</td>
<td>36-125</td>
<td>25-145</td>
</tr>
<tr>
<td>0.06 mg</td>
<td>N</td>
<td>10</td>
<td>10</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>100.1</td>
<td>98.6</td>
<td>83.1</td>
<td>72.5</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>90.0</td>
<td>100.0</td>
<td>72.5</td>
<td>55.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>36.8</td>
<td>34.1</td>
<td>41.2</td>
<td>46.6</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>65-190</td>
<td>55-175</td>
<td>45-165</td>
<td>30-160</td>
</tr>
<tr>
<td>0.4 mg</td>
<td>N</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>86.9</td>
<td>68.4</td>
<td>67.4</td>
<td>51.4</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>92.5</td>
<td>67.5</td>
<td>65.0</td>
<td>45.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>17.6</td>
<td>30.8</td>
<td>20.8</td>
<td>25.1</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>49-105</td>
<td>30-130</td>
<td>40-104</td>
<td>19-85</td>
</tr>
</tbody>
</table>

ANOVA overall p-value: <0.001 <0.001 0.026 <0.001

Dunnett's p-values (one-sided)

- 0.02 mg vs. placebo: 0.002 <0.001 0.033 0.019
- 0.06 mg vs. placebo: <0.001 <0.001 0.073 0.003
- 0.4 mg vs. placebo: <0.001 <0.001 0.006 <0.001

There were no dose-related trends in the number or type of adverse events. The severity of each adverse event was rated as mild.
In summary, the dose of 0.4 mg phentolamine reduced the duration of soft-tissue anaesthesia with no apparent risks to safety. Recovery to normal sensation in the lower lip, chin, tongue, and teeth was faster in phentolamine treated subjects compared to placebo controls. The doses of 0.02 and 0.06 mg also reversed soft-tissue anaesthesia significantly faster than placebo treatment, but with somewhat longer recovery times than in the 0.4 mg treatment group. The number of adverse events in this study was few, and the profile of adverse events in treated groups was not significantly different than in the placebo group. Cardiovascular measures such as heart rate, blood pressure, and ECG rhythm were not affected by phentolamine.

It was concluded that phentolamine produced a dose-dependent increase in the speed of recovery of normal sensation to the lips, teeth, tongue, and chin. No dose related adverse events were seen.

It is noted that there is a large difference in dose between the 0.06mg dose and the 0.4mg doses studied. While there is a dose related improvement seen in recovery time, there is clearly not a linear dose-response relationship. A very similar mean lip recovery time was seen in the 0.2mg study (Dose Ranging Study 1): 82.5mins vs 86.9mins for the 0.4mg dose.

**Dose Ranging Study 3 – Maxillary**

This was a dose-ranging, single centre, double-blind, randomised, placebo-controlled study of the safety and efficacy of a single injection of phentolamine mesilate in the maxillary region of healthy subjects.

Thirty-two subjects (16 male, 16 female) received a maxillary lateral incisor infiltration using 1.8 mL of 2% lidocaine (36 mg) with 1:100,000 epinephrine (18 μg). All subjects completed the trial. Subjects were randomly assigned to receive a single injection of placebo (1.8 mL), 0.02 mg of phentolamine mesilate (1.8 mL of a 0.011 mg/mL solution), 0.08 mg of phentolamine mesilate (1.8 mL of a 0.044 mg/mL solution), or 0.4 mg of phentolamine mesilate (1.8 mL of a 0.2267 mg/mL solution) at 40 minutes after administration of the local anaesthetic, in the same site where the anaesthetic was injected. Randomisation was 1:1:1:1.
All subjects were asked to rate sensation in the upper lip, nose and teeth by self-palpation at 5 minutes before study drug injection (i.e., 35 minutes after anaesthetic), and at 5-minute intervals beginning 5 minutes after study drug injection until all subjects had achieved the return of normal sensation.

Sensation was assessed in the upper lip by pinching with 2 fingers (or thumb and forefinger), in the teeth by biting (bringing the teeth together) and moving the teeth from side to side when the teeth are brought together, and in the nose by pressing the left side of the nose with the forefinger. Responses for the upper lip, nose, and teeth were recorded separately and categorised as 1) numb (no feeling), 2) feeling of pins and needles (tingling), or 3) normal sensation. Responses for the teeth were recorded separately and categorised as 1) numb (no feeling) or 2) normal sensation.

The time to return to normal sensation was measured by counting the minutes from study drug injection to the first time the subject reported normal sensation in a tissue that had been anaesthetised. The primary efficacy endpoint was time to the return of normal sensation in the upper lip. Secondary endpoints were time to the return of normal sensation in the nose and teeth.

The time to the return of normal sensation was analysed with an analysis of variance (ANOVA) for each tissue (lip, nose, teeth) followed by Dunnett’s test to determine the significance of differences between the placebo group and phentolamine-treated groups. The factors in each ANOVA were dose group and subject. Comparisons with a p value of 0.05 or less were considered significantly different.
The primary results were as follows:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Statistical Parameter</th>
<th>Lip</th>
<th>Note</th>
<th>Toosh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>N</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>153.0</td>
<td>126.9</td>
<td>109.1</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>170.0</td>
<td>125.0</td>
<td>95.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>46.3</td>
<td>52.5</td>
<td>71.3</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>85-220</td>
<td>40-215</td>
<td>44-275</td>
</tr>
<tr>
<td>0.02 mg</td>
<td>N</td>
<td>8</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>113.1</td>
<td>75.7</td>
<td>84.1</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>117.5</td>
<td>60.0</td>
<td>70.5</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>50.5</td>
<td>62.2</td>
<td>49.6</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>25-175</td>
<td>20-205</td>
<td>45-190</td>
</tr>
<tr>
<td>0.08 mg</td>
<td>N</td>
<td>7</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>114.9</td>
<td>84.0</td>
<td>51.3</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>110.0</td>
<td>92.0</td>
<td>55.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>38.8</td>
<td>43.5</td>
<td>15.3</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>60-185</td>
<td>15.145</td>
<td>25.70</td>
</tr>
<tr>
<td>0.4 mg</td>
<td>N</td>
<td>8</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>87.6</td>
<td>69.5</td>
<td>43.9</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>87.5</td>
<td>67.3</td>
<td>42.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>50.2</td>
<td>42.3</td>
<td>16.5</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>22-160</td>
<td>17.135</td>
<td>22.75</td>
</tr>
<tr>
<td>ANOVA overall p-value</td>
<td></td>
<td>0.057</td>
<td>0.135</td>
<td>0.034</td>
</tr>
<tr>
<td>Dunnett's p-value (one-sided)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.02 mg vs. placebo</td>
<td></td>
<td>0.110</td>
<td>0.076</td>
<td>0.357</td>
</tr>
<tr>
<td>0.08 mg vs. placebo</td>
<td></td>
<td>0.138</td>
<td>0.150</td>
<td>0.033</td>
</tr>
<tr>
<td>0.4 mg vs. placebo</td>
<td></td>
<td>0.011</td>
<td>0.038</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Again, there were no dose-related trends in the number or type of adverse events. The severity of each adverse event was rated as mild.
Phentolamine at the dose of 0.4 mg reduced the duration of soft-tissue anesthesia with no apparent risks to safety. Recovery to normal sensation in the upper lip, nose and teeth was nearly twice as fast in phentolamine-treated subjects compared to placebo controls. The reductions were approximately one hour in length and were statistically significant in the lip and the teeth. The doses of 0.02 and 0.08 mg did not significantly reduce recovery times. The number of adverse events in this study was few, and the profile of adverse events in treated groups was not reliably different than in the placebo group. Cardiovascular measures such as heart rate, blood pressure and ECG rhythm were not affected by phentolamine.

A similar dose response trend is seen, this time following a maxillary lateral incisor infiltration, and the 0.4 mg dose is seen to significantly reduce the time to recovery of normal sensation in the upper lip and teeth. Again, there were few adverse events and these were not dose related.

Dose ranging studies – conclusion

Overall, it can be agreed that of all the doses studied (0.02 mg, 0.06 mg, 0.08 mg, 0.2 mg and 0.4 mg), the 0.4 mg dose produces the greatest improvement in recovery time. However, although dose dependent this improvement does not display a linear correlation to the dose given. The 0.2 mg dose appeared to provide a similar degree of improvement.

Pharmacokinetics

Two PK studies of phentolamine were conducted:
- one in paediatric dental subjects in which doses of 0.2 mg and 0.4 mg were tested
- one in adult healthy subjects in which doses of 0.4 mg and 0.8 mg were tested.

Pharmacokinetic Study 1

This study was designed as a single centre, open-label, 4-treatment, 4-period, crossover study designed to evaluate the PK, PD, and safety of the test product when administered as an intraoral injection following local anesthesia with 2% lidocaine hydrochloride (HCl) with 1:100,000 epinephrine and when administered as an IV injection over 1 minute.
16 healthy adults (7 male and 9 female), aged between 18 and 50 years were enrolled in the study. Each subject received 4 treatments (A, B, C, and D) in 1 of 4 sequences. The 4 treatments were as follows:

**Treatment A:** Subjects received 1 cartridge of 2% lidocaine HCl with 1:100,000 epinephrine ("anaesthetic"; 1.8 mL), given as a supraperiosteal infiltration over the first molar in the maxilla. Subjects received 1 cartridge of the test product (0.4 mg phentolamine in 1.7 mL) in the same location as the anaesthetic 30 minutes later.

**Treatment B:** Subjects received 1 cartridge of the test product (0.4 mg in 1.7 mL) injected IV over 1 minute. A local anaesthetic was not administered as part of this treatment.

**Treatment C:** Subjects received 4 cartridges of 2% lidocaine HCl with 1:100,000 epinephrine: 3.6 mL administered as an inferior alveolar nerve block and 3.6 mL administered as a supraperiosteal infiltration over the first molar in the maxilla. These injections were administered in the same side of the face. Thirty (30) minutes after the first injection of anaesthetic, 1 cartridge of the test product (1.7 mL) was injected at each site where anaesthetic was given, using the same injection technique. The total dose of phentolamine in this treatment was 0.8 mg (3.4 mL).

**Treatment D:** Treatment D served as a control for Treatment C. Subjects received 4 cartridges of 2% lidocaine HCl with 1:100,000 epinephrine: 3.6 mL administered as an inferior alveolar nerve block and 3.6 mL administered as a supraperiosteal infiltration over the first molar in the maxilla. These 2 injections were administered in the same side of the face. The test product was not administered to subjects in this treatment.

Subjects received 2 of the 4 treatments during each of 2 clinic admissions. Each admission lasted for 2 full days (2 overnights). There was a 24 hour washout period between each treatment.

Blood samples were drawn for measurements of concentrations of phentolamine, lidocaine, epinephrine, and N1-2[N-(3-hydroxyphenyl)- N-(4-toluyl)aminoacetyl] ethylenediamine (HTAEDA). HTAEDA is formed spontaneously in aqueous solutions of phentolamine. Measurement of HTAEDA was included in this study to assess its potential formation in the body. Plasma concentrations of phentolamine, lidocaine and HTAEDA were performed by LC/MS/MS using a validated analytical technique. The LLOQ for phentolamine and lidocaine was 1.0ng/ml and that for HTAEDA was 2.0 ng/ml.

Eleven (Treatment B) or 14 (Treatments A, C and D) blood samples were drawn for PK analysis, starting immediately prior to first injection of local anaesthetic (if given) or injection of the test product, and ending 8.5 hours after the first injection of local anaesthetic (if given) and/or 8 hours after injection of the test product. Per protocol, only selected samples were assayed for epinephrine.

The following PK parameters were estimated for phentolamine, lidocaine, and epinephrine: peak plasma concentration (Cmax), time to peak plasma concentration (Tmax), the area under the plasma concentration-time curve from 0 to the last time-point with measurable concentration (AUClast), the area under the plasma concentration-time curve from time 0 to infinity (AUCinf), elimination half-life (t½), clearance (CL), and the volume of distribution (Vd). All PK parameters were estimated based on noncompartmental methods.
The PD endpoints were the times to normal sensation in the upper lip, lower lip and tongue in subjects who experienced numbness and/or tingling in these sites.

The results were as follows:

<table>
<thead>
<tr>
<th>Study Treatment (Phentolamine)</th>
<th>Study Treatment (Lidocaine)</th>
<th>Study Treatment (Liposome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Cmax, ng/mL</td>
<td>1.24</td>
<td>0.10</td>
</tr>
<tr>
<td>AUC0-5h/mL</td>
<td>1.69</td>
<td>0.21</td>
</tr>
<tr>
<td>T1/2, h</td>
<td>0.20</td>
<td>0.01</td>
</tr>
<tr>
<td>CL, L/min</td>
<td>1.00</td>
<td>0.10</td>
</tr>
<tr>
<td>Vd, L</td>
<td>0.25</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* Please note that for treatment C, PK results were obtained from 15 subjects instead of 16. The protocol and analysis plan considered a subject evaluable for PK analysis in any treatment arm if at least 80% of the scheduled blood draws yielded at least 4 ml of blood to be assayed. Data from Treatment C for one subject were excluded from the PK analysis because no post-baseline PK blood samples were obtained. Blood samples could not be drawn for this subject after Treatment C because a collapsed vein resulted in loss of venous access.

**Phentolamine PK parameters:** Treatments A, B and C were evaluated for phentolamine PK parameters. (No test product was administered in Treatment D.) The phentolamine Cmax values for Treatments A and C were dose-proportional, with twice the amount injected resulting in approximately twice the Cmax.

Although the same amount of phentolamine was injected in Treatments A and B, the phentolamine Cmax value for Treatment B (IV injection) was 8 times larger than the value for Treatment A (intraoral mucosal injection). The phentolamine AUC0-5h and AUCinf values were dose proportional, with Treatments A and B similar in value and Treatment C approximately twice the value of Treatments A and B.

The phentolamine T1/2 was earlier for Treatment B (7 minutes) than for Treatments A (15 minutes) or C (11 minutes). The phentolamine T1/2, CL, and Vd values were similar for Treatments A, B and C. Phentolamine was completely bioavailable after intraoral injection (Treatment A) (90% or 111 %, using linear or log trapezoidal methods, respectively, for AUC calculation, compared to its bioavailability after intravenous injection (Treatment B).
The plasma concentrations of HTAEDA were almost entirely below the limit of quantitation. Therefore, PK parameters were not estimated for HTAEDA.

**Lidocaine PK parameters:** Treatments A, C and D were evaluated for lidocaine PK parameters. (No local anesthesia was administered in Treatment B.) The lidocaine \( C_{\text{max}} \), \( \text{AUC}_{\text{last}} \) and \( \text{AUC}_{\text{inf}} \) values were all dose proportional, with similar values for Treatments C and D, and values for Treatment A that were approximately one-fourth the values of Treatments C and D. The lidocaine \( T_{\text{max}} \) and CL values were similar for Treatments A, C and D.

The \( T_{\text{max}} \) for lidocaine was statistically significantly later in Treatment C than in Treatment D. The lidocaine \( V_d \) value was statistically significantly smaller in Treatment C than in Treatment D.

The phentolamine-induced delay of the lidocaine \( T_{\text{max}} \) in Treatment C, relative to Treatment D, is a demonstration of phentolamine's ability to accelerate the clearance of lidocaine from oral tissues into the circulatory system. The observed difference in lidocaine \( V_d \), 192 litres in Treatment C and 237 litres in Treatment D, although statistically significant, is not clinically meaningful because neither \( C_{\text{max}} \) nor AUC values differed significantly between these two treatments.

**Epinephrine PK parameters:** Treatments C and D were evaluated for epinephrine PK parameters. The epinephrine \( C_{\text{max}} \), \( T_{\text{max}} \), \( \text{AUC}_{\text{last}} \), \( \text{AUC}_{\text{inf}} \), \( T_{\text{max}} \) and \( V_d \) values were all similar among treatment groups.

The epinephrine CL for Treatment C was statistically significantly smaller than the epinephrine CL for Treatment D. The decreased clearance of epinephrine in Treatment C relative to Treatment D, although statistically significant, is not considered to be clinically meaningful. Epinephrine clearance could be calculated for only 8 of the 16 subjects and might thus be a biased estimate of epinephrine clearance.

**Pharmacodynamics:** the time to return of normal sensation was evaluated relative to the time of the test product injection. As no test product was administered under Treatment D the time to normal sensation ("adjusted time") was calculated relative to the injection time of the local anaesthetic plus a constant equal to the mean time between the first injection of local anaesthetic and first injection of the test product for Treatment C.

By 60 minutes after injection of the test product for Treatments A and C or "adjusted time" for Treatment D, the percentage (%) of evaluable subjects with normal sensation in the upper lip was markedly greater with Treatments A and C than with Treatment D. By 90 minutes after injection of the test product for Treatment C, all evaluable subjects had normal sensation in the upper lip, with maintenance of normal upper lip sensation through the rest of the 5-hour follow-up period. After Treatment A, all evaluable subjects had normal upper lip sensation by 170 minutes after injection of the test product. In contrast, with Treatment D, not until 230 minutes "adjusted time" did all evaluable subjects regain normal upper lip sensation. Consistent with these findings, the median time to normal sensation of the upper lip for Treatment D was approximately twice as long as the median time for Treatments A or C.

The sensation rating for the lower lip was evaluated for Treatments C and D (both mandibular and maxillary injections), but not for Treatments A (maxillary injection) and B.
(IV injection). Only subjects who experienced numbness and/or tingling in their lower lip were evaluable for return of normal sensation in the lower lip. All evaluable subjects regained normal lower lip sensation after Treatment C by 170 minutes after dosing with the test product. In contrast, with Treatment D, at the 170 minute "adjusted time" time point only approximately 10% of evaluable subjects had regained normal lower lip sensation, and by 250 minutes "adjusted time" to the end of the 300-minute "adjusted-time" follow-up period, only approximately 80% of evaluable subjects had regained normal lower lip sensation. Consistent with these findings, the median time to normal sensation of the lower lip for Treatment D was approximately twice as long as the median time for Treatment C.

The sensation rating for the tongue was evaluated for Treatments C and D (both mandibular and maxillary injections), but not for Treatments A (maxillary injection) and B (IV injection). Only subjects who experienced numbness and/or tingling in their tongue were evaluable for return of normal sensation in the tongue.

All evaluable subjects regained normal tongue sensation after Treatment C by 160 minutes after dosing with the test product. In contrast, with Treatment D, at the 160 minute "adjusted-time" time point only approximately 25% of evaluable subjects had regained normal tongue sensation, and from 260 minutes "adjusted time" to the end of the 300-minute "adjusted-time" follow-up period, approximately 95% of evaluable subjects had regained normal tongue sensation. Consistent with these findings, the median time to normal sensation of the tongue for Treatment D was approximately twice as long as the median time for Treatment C.

**Safety:** There were no deaths or serious adverse events reported during this study. No subjects discontinued due to adverse events. Similar numbers of subjects reported all-causalities adverse events during each of the treatments. The largest number of all causalities adverse events was reported after Treatment D (no test product administered), while the smallest number was reported after Treatment B (one cartridge of the test product administered).

### Adverse Event

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Study Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A N = 16</td>
</tr>
<tr>
<td>(Preferred Term)</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>5 (3*)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>4 (2*)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (1*)</td>
</tr>
<tr>
<td>Parasthesia</td>
<td>0 (0*)</td>
</tr>
<tr>
<td>Facial pain</td>
<td>1 (0*)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0*)</td>
</tr>
<tr>
<td>Pain in jaw</td>
<td>0 (0*)</td>
</tr>
</tbody>
</table>

A = 1 cartridge of local anesthetic and 1 cartridge of NV-101; B = 1 cartridge of IV injection of NV-101; C = 4 cartridges of local anesthetic and 2 cartridges of NV-101; D = 4 cartridges of local anesthetic.

*Treatment-related = related to study injection.

**Study Conclusion**

From this study it is agreed that the PK results for phentolamine show dose proportionality and the presence of phentolamine would appear to increase the clearance of lidocaine from the oral tissues. The PD results are supportive, although this study was not an efficacy trial.
It is reassuring that there were no dose related adverse effects seen and, of note, the adverse event profile was no worse in Treatment B despite the higher $C_{\text{max}}$ associated with the IV administration.

**Pharmacokinetic Study 2**

This was a Phase I, multicenter, open-label study of the test product (phentolamine mesilate) to evaluate the PK and safety of the test product in paediatric patients aged 3 – 17 years who were undergoing dental procedures under general anaesthesia or conscious sedation and who required an IV line. All subjects were also administered local anaesthetic consisting of 2% lidocaine with 1:100,000 epinephrine.

The test product was administered by submucosal injection approximately 30 minutes after the injection of 2% lidocaine with 1:100,000 epinephrine and completion of the dental procedure, using the same location and same technique used for the administration of the local anaesthetic. The dose of local anaesthetic (2% lidocaine with 1:100,000 epinephrine) and the test product depended upon the weight of the subject. For subjects in both weight groups, the volume of the dose of local anaesthetic was equal to the volume of the test product as follows:

- Subjects weighing $\geq 15$ kg and $< 30$ kg received a half cartridge of 2% lidocaine with 1:100,000 epinephrine and a half cartridge (0.2 mg phentolamine mesilate) of the test product.

- Subjects weighing $\geq 30$ kg received a whole cartridge of 2% lidocaine with 1:100,000 epinephrine and a whole cartridge (0.4 mg phentolamine mesilate) of the test product.

If additional injections of local anaesthetic were required for dental procedures elsewhere in the oral cavity, additional injections of 2% mepivacaine with 1:20,000 levonordefrin or 3% mepivacaine were permitted.

The following patients were recruited:

<table>
<thead>
<tr>
<th>NV-101 Dose Group</th>
<th>3-6 years</th>
<th>7-11 years</th>
<th>12-17 years</th>
<th>Overall N=19</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 mg N=6</td>
<td>0.2 mg N=2</td>
<td>3.4 mg N=4</td>
<td>0.2 mg N=0</td>
<td>0.4 mg N=7</td>
</tr>
<tr>
<td>Number of subjects &amp; (%)</td>
<td>6 (100.0)</td>
<td>2 (100.0)</td>
<td>4 (100.0)</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td>Enrolled subjects</td>
<td>6 (100.0)</td>
<td>2 (100.0)</td>
<td>4 (100.0)</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td>Treated subjects</td>
<td>6 (100.0)</td>
<td>2 (100.0)</td>
<td>4 (100.0)</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td>Completed assessments</td>
<td>6 (100.0)</td>
<td>2 (100.0)</td>
<td>4 (100.0)</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (100.0)</td>
<td>2 (100.0)</td>
<td>4 (100.0)</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td>No</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (0.0)</td>
<td>3 (0.0)</td>
</tr>
</tbody>
</table>

Please note that the test product on the table is shown as NV-101.

For PK evaluation, venous blood samples of 2 mL each were obtained using the indwelling IV line: 1 sample prior to injection of the test product and then at 5, 10, 15, 20, 30, and 45 minutes, and at 1.0, 1.5, 2.0 and 3.0 hours following administration of the test product. A final blood sample was taken immediately before IV line removal. The maximum total volume of blood drawn did not exceed 22 mL. Removal of the IV line prior to the 2- and 3-
hour sampling points reduced the numbers of subjects included in pharmacokinetic analyses at those time points. Among the 0.2 mg dose group, 7 out of 8 subjects were sampled at 2 hours after dosing, but only 1 out of 8 subjects at the 3-hour point. Among the 0.4 mg dose group, samples were obtained from 11 out of 11 subjects at 2 hours, and from 10 out of 11 subjects at 3 hours. Blood samples were obtained from all subjects at all other scheduled time points.

Concentrations of phentolamine and lidocaine were determined in each sample with a validated assay. To the extent possible with limited duration of sampling, the pharmacokinetics of phentolamine were calculated. The pharmacokinetics of lidocaine were not calculated.

Results

The majority of the subjects (87.5%) in the 0.2 mg dose group received general anaesthesia, while all subjects (100%) in the 0.4 mg dose group received conscious sedation. In addition, most of the subjects (75%) in the 0.2 mg dose group received additional local anaesthetic, in contrast to the 0.4 mg group (27.3%).

The dosing scheme planned for this study was based on body weight and was intended to achieve similar average weight-based dose levels in the two groups (those greater than 30 kg and those less than 30 kg). With an even distribution of body weights of children, the target average dose was expected to be 0.010 mg/kg. The actual doses based on body weight were as follows:

<table>
<thead>
<tr>
<th>NV-101 Dose</th>
<th>Subject I.D.</th>
<th>Body Weight (kg)</th>
<th>Weight/Weight Dose (mg/kg)</th>
<th>Subject I.D.</th>
<th>Body Weight (kg)</th>
<th>Weight/Weight Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 mg</td>
<td>01-001</td>
<td>20</td>
<td>0.0100</td>
<td>03-001</td>
<td>127</td>
<td>0.0031</td>
</tr>
<tr>
<td></td>
<td>01-002</td>
<td>17</td>
<td>0.0118</td>
<td>03-002</td>
<td>30</td>
<td>0.0133</td>
</tr>
<tr>
<td></td>
<td>01-003</td>
<td>15</td>
<td>0.0125</td>
<td>03-003</td>
<td>67</td>
<td>0.0060</td>
</tr>
<tr>
<td></td>
<td>01-004</td>
<td>25</td>
<td>0.0080</td>
<td>03-004</td>
<td>50</td>
<td>0.0080</td>
</tr>
<tr>
<td></td>
<td>02-001</td>
<td>24</td>
<td>0.0083</td>
<td>03-005</td>
<td>48</td>
<td>0.0083</td>
</tr>
<tr>
<td></td>
<td>02-002</td>
<td>21</td>
<td>0.0095</td>
<td>03-006</td>
<td>78</td>
<td>0.0051</td>
</tr>
<tr>
<td></td>
<td>02-003</td>
<td>15</td>
<td>0.0125</td>
<td>03-007</td>
<td>49</td>
<td>0.0082</td>
</tr>
<tr>
<td></td>
<td>03-012</td>
<td>25</td>
<td>0.0077</td>
<td>03-008</td>
<td>41</td>
<td>0.0098</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>03-009</td>
<td>36</td>
<td>0.0111</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>03-010</td>
<td>47</td>
<td>0.0085</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>03-011</td>
<td>37</td>
<td>0.0108</td>
</tr>
<tr>
<td>Mean</td>
<td>20.525</td>
<td>0.0100</td>
<td>Mean</td>
<td>55.455</td>
<td>0.0084</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>16-26</td>
<td>0.0077-0.0125</td>
<td>Range</td>
<td>30-127</td>
<td>0.0031-0.0133</td>
<td></td>
</tr>
</tbody>
</table>

Please note that the test product on the table is shown as NV-101.

The mean dose in the lighter-weight group (0.0100 mg/kg) was on target but the mean dose of the larger children (0.0084 mg/kg) was slightly below the target. This difference in dose level was not reflected in AUC values for the two groups as these parameters were remarkably equal between the groups. However, $C_{max}$ values were lower in the heavier weight group. The greater mean Vd in the 0.4 mg dose group is consistent with the greater mean body weight in this dose group.
The incidence of all-causality adverse events was low, and all 5 events were experienced by 4 subjects in the 0.4-mg dose group. Adverse events recorded were vomiting, oral pain, post-procedural pain and headache. All of the events were rated as moderate in severity, except for 1 incidence of post-procedural pain that was rated as mild in severity.

The pharmacokinetic profile of phentolamine after intraoral injection in paediatric dental patients, indicates that systemic exposure is brief and at low levels. This is consistent with the low incidence of safety findings in this study. The test product was well-tolerated at the doses administered in this study.
Study Conclusion
The mean $C_{\text{max}}$ value (1.47 ng/mL) in children dosed with 0.4 mg was similar to the mean $C_{\text{max}}$ (1.34 ng/mL) in adults given the same dose in Pharmacokinetic Study 1. The individual $C_{\text{max}}$ values had similar ranges as well (paediatrics, 0.9 to 2.2 ng/mL versus adults, 0.46 to 1.88 ng/mL).

The mean $C_{\text{max}}$ of phentolamine in children dosed with 0.2 mg (2.60 ng/mL) is similar to that of adults dosed with 0.8 mg (2.73 ng/mL). However, this can be mainly attributed to the weight based dosing scheme used in the paediatric study.

The level of systemic exposure seen following intraoral injection of the test product in both adults and children is low and the drug seems to be well tolerated. Of note, no comment was made in the study report on the nature of the procedures being performed in the paediatric study. Therefore, one cannot comment on the side effect of pain in relation to a specific procedure type. However, as a PK study, these results are supportive.

Phase I/II Studies - Conclusion
The applicant has provided dose ranging studies examining the preliminary efficacy and safety of a range of doses from 0.02mg to 0.8mg.

Phentolamine is seen to be completely bioavailable following intraoral mucosal injection and there is an essentially linear dose-dependent increase in exposure and this is consistent across the ages ranges seen. However, the exposure remains low and this is consistent with the low frequency of adverse events seen.

However, the same linearity is not seen in regard to the dose-response relationship. The difference in mean time to recovery of normal lip sensation between the various doses of phentolamine mesilate and placebo following one cartridge of anaesthetic is seen below:

<table>
<thead>
<tr>
<th>Phentolamine Mesylate Dose</th>
<th>Study</th>
<th>Mean Reduction (minutes)</th>
<th>Percent Reduction Compared to Placebo</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2mg Dose-Ranging Study 2</td>
<td>53.0</td>
<td>34%</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>0.2mg Dose-Ranging Study 3</td>
<td>39.9</td>
<td>26</td>
<td>0.110</td>
<td></td>
</tr>
<tr>
<td>0.06mg Dose-Ranging Study 2</td>
<td>57.5</td>
<td>36</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>0.08mg Dose-Ranging Study 3</td>
<td>38.1</td>
<td>25</td>
<td>0.138</td>
<td></td>
</tr>
<tr>
<td>0.2mg Dose-Ranging Study 1</td>
<td>58.0</td>
<td>41</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>0.4mg Dose-Ranging Study 2</td>
<td>70.7</td>
<td>45</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>0.4mg Dose-Ranging Study 3</td>
<td>65.4</td>
<td>43</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>0.4mg Phase II Study 1</td>
<td>64.7</td>
<td>43</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>0.8mg Phase II Study 1</td>
<td>87.4</td>
<td>49</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>0.4mg and 0.8mg (combined)</td>
<td>76.0</td>
<td>46</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
Based on the above, the dose of 0.4 mg was appropriately selected for further evaluation in the Phase III studies for 4 reasons:

- The efficacy results produced both a mean reduction in time to normal sensation compared to placebo that was greater than 1 hour and a percent reduction that was nearly 50%,

- The efficacy results were consistent in the 3 studies in which that dose was evaluated,

- The safety results were comparable for 0.4 mg and the lower doses,

- The number of subjects exposed to a dose of 0.4 mg was greater than all lower doses combined (80 vs. 45 subjects), providing a stronger basis for evaluating this dose in the Phase III studies.

The 0.4mg dose showed the greatest efficacy as defined by mean reduction in time to normal sensation of the doses studied at Phase II. This was seen with a comparable safety profile to the 0.2mg dose. The absence of data at the 0.2mg dose, cannot be considered to represent a safety risk.

**Efficacy**

The applicant has conducted two Phase III placebo controlled trials examining the efficacy of the test product. Two supportive Phase II trials in dental patients are also presented and a solely paediatric efficacy trial.

The drug product used in both Phase III studies in adult and adolescent subjects and that in the Phase II paediatric study is the final version of the test product. The drug product tested in Phase II study 1 was an ‘initial’ test product solution of phentolamine mesilate dosed at 0.222 mg/ml as opposed to 0.235 mg/ml in the final formulation.

**Phase II Studies**

**Phase II Study 1**

This was a multicentre, double blind, randomised, placebo controlled study designed to evaluate the efficacy of the test product in reducing the duration of local anaesthesia in the lip, chin, nose and tongue following injection by any one of four local anaesthetic agents formulated with a vasoconstrictor.

One hundred and twenty-two patients were enrolled who required treatment with one of four routine dental procedures that included and were limited to:

1) teeth cleaning
2) scaling and planing
3) cavity filling
4) crowns

The investigators were licensed dentists in private practice. Each patient received one or more conventional injections of either articaine with epinephrine, lidocaine with epinephrine, prilocaine with epinephrine, or mepivacaine with levonordefrin. Local anaesthetics were
injected into no more than 2 sites. Injections of local anaesthetic placed within 4 mm of each other constituted the same site.

Each maxillary patient received a conventional supraperiosteal infiltration or anterior or middle superior alveolar nerve block as appropriate to their planned dental treatment, with one of the selected local anaesthetic products. Each mandibular patient received a conventional IANB, as appropriate to his or her planned dental treatment. Numbness of the lip (maxillary) or lower lip and chin (mandibular) was assessed at 5 minute intervals following the injection of local anaesthetic until 10 minutes and 20 minutes respectively. If insufficient anaesthesia was present to carry out the procedure at these time points then the patient was discontinued from the study.

If the procedure required multiple injections of local anaesthesia, the patient could remain in the study as long as:

1. No more than two sites were used for injection of anaesthetic
2. A second injection site was used only as required to induce sufficient pulpal anaesthesia to initiate the procedure
3. The second injection must have been made in a different location than the first injection and it must have been made within 20 minutes after the first injection
4. Patients affirmed that their lip was numb at 10 minutes after the injection of anaesthetic given in the second site (or lower lip and chin at 20 minutes for a mandibular procedure)
5. Injections of anaesthetic given more than 20 minutes after the first injection were only allowed for crown procedures and must have been made in a site that had previously been used for anaesthetic injection.

Subsequently, patients received an injection of the test product (1.8 mL) in each site at which local anaesthetic had been injected (i.e., no more than 2 sites). The injection(s) of study drug were made at or near the completion of the dental procedure. These injections were made not earlier than 20 minutes, and not later than 70 minutes after the most recent injection of local anaesthetic, regardless of site. In cases of multiple-site injections of anaesthetic, study drug was administered to each site in quick succession. Thus, if anaesthetic was given to a second site at 15 minutes after it was injected into the first site, the 20-70 minute window was based on the time of the second injection of anaesthetic and the two injections of study drug were given one right after the other.

Patients receiving maxillary dental procedures self-evaluated the return of normal sensation in the upper lip and nose by palpations at 5-minute intervals beginning 1 minute before study drug injection and continuing for a minimum of 3 hours or until the return of normal sensation in both the lip and nose. Mandibular patients self-evaluated the return of sensation in an identical manner except that the lower lip, chin and tongue were evaluated and not the upper lip or nose. In both cases, the primary endpoint was the time to return of normal sensation in the lip (upper or lower).

Sensation was assessed in the lip by pinching with 2 fingers (or thumb and forefinger), in tongue by pinching the lateral edge of the tongue while extruding the tongue outside the mouth, and in the chin and nose by pressing with the forefinger. Responses were recorded separately for each tissue and categorised as numb (no feeling), feeling of pins and needles or normal sensation.
A total of 122 patients, 68 female and 54 male were included in this study. Their ages ranged from 10 – 61 years. Patients were randomised to either placebo or the test product resulting in equal sized groups of 61. There was also a fairly equal spread of choice of local anaesthetic used and type of procedure:

<table>
<thead>
<tr>
<th>Gender</th>
<th>Placebo lidocaine (n=15)</th>
<th>Placebo articaine (n=15)</th>
<th>Placebo prilocaine (n=13)</th>
<th>Mepivacaine (n=18)</th>
<th>NV-101 (0.4 mg) lidocaine (n=15)</th>
<th>NV-101 (0.4 mg) articaine (n=15)</th>
<th>NV-101 (0.4 mg) prilocaine (n=13)</th>
<th>NV-101 (0.4 mg) mepivacaine (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>11</td>
<td>6</td>
<td>5</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>7</td>
<td>9</td>
<td>10</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filipino</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polynesian</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>15</td>
<td>13</td>
<td>13</td>
<td>17</td>
<td>15</td>
<td>10</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>White/Black</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>27.5</td>
<td>25.3</td>
<td>31.7</td>
<td>23.5</td>
<td>24.9</td>
<td>28.2</td>
<td>25.7</td>
<td>29.5</td>
</tr>
<tr>
<td>Minimum</td>
<td>12</td>
<td>17</td>
<td>16</td>
<td>12</td>
<td>12</td>
<td>19</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Maximum</td>
<td>54</td>
<td>56</td>
<td>58</td>
<td>50</td>
<td>47</td>
<td>56</td>
<td>42</td>
<td>61</td>
</tr>
<tr>
<td>Height (in.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>66.7</td>
<td>67.0</td>
<td>68.5</td>
<td>65.3</td>
<td>68.4</td>
<td>69.9</td>
<td>65.3</td>
<td>66.8</td>
</tr>
<tr>
<td>SD</td>
<td>4.60</td>
<td>3.22</td>
<td>2.89</td>
<td>3.52</td>
<td>3.91</td>
<td>5.02</td>
<td>3.35</td>
<td>3.60</td>
</tr>
<tr>
<td>Minimum</td>
<td>58</td>
<td>61</td>
<td>63.5</td>
<td>59</td>
<td>62</td>
<td>61.5</td>
<td>59</td>
<td>62</td>
</tr>
<tr>
<td>Maximum</td>
<td>73</td>
<td>73</td>
<td>74</td>
<td>72</td>
<td>75</td>
<td>80.5</td>
<td>70.5</td>
<td>74</td>
</tr>
<tr>
<td>Weight (lbs.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>154.6</td>
<td>169.1</td>
<td>179.2</td>
<td>162.2</td>
<td>162.5</td>
<td>184.5</td>
<td>155.2</td>
<td>181.2</td>
</tr>
<tr>
<td>SD</td>
<td>41.26</td>
<td>37.93</td>
<td>30.59</td>
<td>34.09</td>
<td>46.28</td>
<td>21.05</td>
<td>42.33</td>
<td>43.60</td>
</tr>
<tr>
<td>Minimum</td>
<td>98</td>
<td>127</td>
<td>139</td>
<td>124</td>
<td>100</td>
<td>150</td>
<td>100</td>
<td>106</td>
</tr>
<tr>
<td>Maximum</td>
<td>232</td>
<td>248</td>
<td>224</td>
<td>249</td>
<td>239</td>
<td>230</td>
<td>227</td>
<td>253</td>
</tr>
</tbody>
</table>

Please note that the test product on the table is shown as NV-101.
The planned analyses were conducted without including the time interval between the anaesthetic injection and the study drug injection. The protocol restricted the administration of study drug to a range of 20 to 70 minutes after anaesthetic injection. The mean intervals for the test product and placebo patients in each anaesthetic product were similar, as follows:

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Placebo</th>
<th>NV-101 (0.4 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
</tr>
<tr>
<td>Articaine</td>
<td>15</td>
<td>46.93</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>15</td>
<td>45.87</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>18</td>
<td>36.61</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>13</td>
<td>41.77</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>42.5</td>
</tr>
</tbody>
</table>

Please note that the test product on the table is shown as NV-101.
The primary results were as follows:

<table>
<thead>
<tr>
<th>Location</th>
<th>Anesthetic</th>
<th>Placebo</th>
<th>NV-101 (0.4 mg)</th>
<th>Difference Between Placebo &amp; NV-101</th>
<th>Percent Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mandible</strong></td>
<td></td>
<td>N</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lidocaine/epinephrine</td>
<td>Mean (min)</td>
<td>155.7</td>
<td>84.6</td>
<td>71.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (min)</td>
<td>65.0</td>
<td>45.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range (min)</td>
<td>95-270</td>
<td>30-155</td>
<td></td>
</tr>
<tr>
<td></td>
<td>anticaine/epinephrine</td>
<td>N</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (min)</td>
<td>169.6</td>
<td>133.9</td>
<td>35.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (min)</td>
<td>45.0</td>
<td>46.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range (min)</td>
<td>109-231</td>
<td>70-200</td>
<td></td>
</tr>
<tr>
<td></td>
<td>prilocaine/epinephrine</td>
<td>N</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (min)</td>
<td>131.4</td>
<td>71.0</td>
<td>60.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (min)</td>
<td>40.7</td>
<td>42.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range (min)</td>
<td>85-189</td>
<td>29-150</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mepivacaine/levonorgestrel</td>
<td>N</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (min)</td>
<td>176.4</td>
<td>120.0</td>
<td>56.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (min)</td>
<td>56.4</td>
<td>42.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range (min)</td>
<td>72-241</td>
<td>60-205</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>Mean (min)</td>
<td>158.3</td>
<td>102.4</td>
<td>55.9</td>
</tr>
<tr>
<td><strong>Maxilla</strong></td>
<td></td>
<td>N</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lidocaine/epinephrine</td>
<td>Mean (min)</td>
<td>130.8</td>
<td>49.6</td>
<td>101.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (min)</td>
<td>33.7</td>
<td>47.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range (min)</td>
<td>106-200</td>
<td>11-150</td>
<td></td>
</tr>
<tr>
<td></td>
<td>anticaine/epinephrine</td>
<td>N</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (min)</td>
<td>173.0</td>
<td>87.8</td>
<td>85.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (min)</td>
<td>29.7</td>
<td>43.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range (min)</td>
<td>110-195</td>
<td>35-166</td>
<td></td>
</tr>
<tr>
<td></td>
<td>prilocaine/epinephrine</td>
<td>N</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (min)</td>
<td>111.2</td>
<td>64.6</td>
<td>46.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (min)</td>
<td>50.8</td>
<td>65.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range (min)</td>
<td>30-170</td>
<td>20-165</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mepivacaine/levonorgestrel</td>
<td>N</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (min)</td>
<td>157.1</td>
<td>79.0</td>
<td>78.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD (min)</td>
<td>67.2</td>
<td>60.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range (min)</td>
<td>50-261</td>
<td>20-180</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>Mean (min)</td>
<td>148.0</td>
<td>70.2</td>
<td>77.8</td>
</tr>
</tbody>
</table>

Please note that the test product on the table is shown as NV-101.

The time to return to normal sensation in patients treated with the test product was reduced by an average of 56 minutes (35%) in the mandible and 78 minutes (53%) in the maxilla compared to placebo (p < 0.001), with an average reduction of 67 minutes (44%) for the combination of upper and lower lips. No significant differences were detected by covariates: age; gender; 1 or 2 injections; type of dental procedure.

The secondary endpoints were the time to return to normal sensation in the chin, tongue and nose. In these domains, the test product significantly reduced the time to return to normal sensation by an average of 48 minutes (35%) in the chin and 37 minutes (32%) in the tongue compared to placebo (p ≤ 0.001 for each tissue). The test product was not significantly better than placebo with regard to sensation in the nose.
The profiles of adverse events in the test product and placebo groups were similar. Cardiovascular measures such as heart rate, blood pressure, and ECG rhythm were not affected by the test product. A statistically significant increase in oral/jaw pain was found in patients one hour after receiving the test product. The average pain rating for the test product in patients at this time point was rated as weak compared to average ratings of none to faint in placebo treated patients. The increased pain felt by patients treated with the test product was brief, dissipated without intervention, and was not considered clinically significant.

**Study Conclusion**

Despite being slightly different from the final formulation, the test product showed a significant improvement in recovery times against four different local anaesthetic combinations and in both IANB and conventional supraperiosteal infiltration or anterior or middle superior alveolar nerve blocks. These improvement times were not only statistically significant but they could also be considered clinically significant.

The only notable adverse event was an increase in mild pain experienced post-procedure, although none of the procedures performed were likely to produce high levels of post-procedural pain.

None of the four permitted procedures could be considered ‘invasive’ either i.e. they were unlikely to be associated with post-procedural bleeding. Therefore no comment can be made on the safety of the product in this regard based on the results of this study.

**Phase II Study 2**

This Phase II, multicentre, randomised, blinded, controlled clinical study was designed to evaluate the safety and efficacy of the test product used for reversal of soft tissue anaesthesia (STA) in paediatric dental subjects 4 to 11 years of age undergoing restorative or periodontal maintenance procedures requiring local anaesthesia with 2% lidocaine + 1:100,000 epinephrine.

Following completion of the dental procedure, eligible subjects were randomised to the test product or control (placebo injection) in a 2:1 allocation ratio, respectively, and stratified according to the location of the dental procedure (mandible or maxilla) and study site. The number of cartridges of the test product or placebo injections was planned to be equal to the number of cartridges of local anaesthetic (2% lidocaine with 1:100,000 epinephrine). Supplemental supraperiosteal injections (infiltrations) of the same anaesthetic were permitted as long as they were not likely to result in STA of the lip and/or tongue and comprised a volume less than 0.6 mL.

Study drug (the test product or placebo) was administered by the same investigator who administered local anaesthetic by submucosal injection after the completion of the dental procedure, using the same location and same technique used for the administration of local anaesthetic.

The study recruited 152 subjects. The treatment groups were well balanced for race, ethnicity, age, grade, height and weight. Nearly equal numbers of males and females were enrolled. About half of the subjects in each treatment group were white, with black/African American subjects as the next most frequent. Subjects were randomised to the test product or control (placebo injection) in a 2:1 allocation ratio, respectively, and stratified according to the location of the dental procedure (mandible or maxilla) and study site.
The doses of local anaesthetic and study drug (the test product or placebo) depended upon the weight of the subject. For subjects in both weight groups, the volume of the dose of local anaesthetic was equal to the volume of the test product as follows:

- Subjects weighing ≥ 15 kg and < 30 kg received a half cartridge of 2% lidocaine with 1:100,000 epinephrine and a half cartridge (0.2 mg phentolamine mesilate) of the test product or a placebo injection.
- Subjects weighing ≥ 30 kg received a half or a whole cartridge of 2% lidocaine with 1:100,000 epinephrine and a whole cartridge (0.4 mg phentolamine mesilate) of the test product or a sham injection.

The primary objective of this study was to evaluate the safety and tolerability of the test product in all subjects as measured by:

- Incidence and severity of adverse events
- Incidence, severity and duration of intraoral pain as measured by the Wong-Baker FACES Pain Rating Scale (W-B PRS)
- Clinically significant changes in vital signs
- Clinically significant changes in oral cavity assessments (OCA)s
- Analgesics required for intraoral pain

The time to return of normal sensation to lip or tongue was a secondary objective measured in subjects 6-11 years of age who were able to be trained in a standardised palpation procedure. The observation period for safety assessments was 2 hours in subjects 4 to 5 years of age who were trainable in the W-B PRS and subjects 6 to 11 years of age who were trainable in the W-B PRS, but not trainable in a standardized palpation procedure.

The observation period for safety and efficacy assessments was 4 hours for subjects 6 to 11 years of age who were trainable in the W-B PRS and a standardized palpation procedure. During this observation period, study procedures were performed by study staff who were blinded to treatment group assignment. Subjects who were discharged less than 4 hours after study drug administration were contacted by telephone on the same day (Day 1) to evaluate adverse events, analgesics required for oral pain, and other concomitant medications. All subjects were contacted by telephone on Day 2 or Day 3 for follow-up of adverse events and concomitant medications.

The number of subjects in the modified ITT (mITT) analysis sets was less than the number of randomised subjects because of the criteria for inclusion in these analysis sets. For the mITT lip sensation analysis set, a total of 37 subjects (24 in the test product group and 13 in the placebo group) were either 4 to 5 years old or 6 to 11 years old and were not trainable in the standardized palpation procedure. These 37 subjects were excluded from this analysis set and were to be analysed for safety only.

The efficacy results therefore consisted of a population of 72 subjects in the test product group and 43 in the placebo group. In the test product group, the median time to normal sensation of the lip was 60 minutes (95% confidence interval: 45 to 75 minutes). In the placebo group, the median time to normal sensation of the lip was 135 minutes (95% confidence interval: 105 to 165 minutes). There was a statistically significant difference (p < 0.0001) in time to recovery of normal sensation of the lip between the test product and sham as analysed by the stratified log-rank test. The stratification factor used in this analysis was
the location of dental procedure (mandibular or maxillary). The reduction in median time to normal sensation of the lip of subjects with the test product (60 minutes) compared to sham (135 minutes) was 75 minutes (55.6%):

Further subgroup analyses demonstrated consistency across the various subsets based on number of cartridges, type of dental procedure, type of nerve block, and sex.

The primary endpoint was safety and tolerability as measured by adverse events, intraoral pain, vital signs, OCAs, and concomitant medications. A total of 35 of the 152 subjects (23.0%) reported 37 adverse events, with similar frequencies in both randomised treatment groups. There were no deaths or other serious adverse events, and no subject was discontinued because of an adverse event. All but 3 adverse events were mild or moderate in severity. There was 1 severe adverse event (post-procedural pain) in subjects randomised to the test product and 2 severe adverse events (injection site pain and post-procedural pain) in subjects randomised to placebo. All adverse events were transient and resolved within the study period.

The majority of adverse events (23/37, 62.2%) were deemed related to study drug, with similar frequency in the 2 treatment groups. Only 1 treatment-related adverse event was severe: severe injection site pain in a subject randomised to placebo. There was a low frequency of all individual treatment-related adverse events.

The most frequently reported treatment-related adverse events were injection site pain, post-procedural pain, increased diastolic blood pressure, and increased blood pressure. The mean values over time for supine/sitting systolic and diastolic blood pressure and pulse were similar for the 2 randomised treatment groups, with only small deviations from the baseline.
values. There was no evidence in this study for an effect of the test product treatment on vital signs.

The incidence of subjects with no intraoral pain (measured by the W-B PRS) was similar in both groups and ranged from approximately 50% to more than 90% at the time points over the 4-hour observation period. The highest mean W-B PRS values were obtained just after administration of local anaesthetic and declined steadily over time. The distribution of most severe intraoral pain scores was similar in subjects randomised to the test product and subjects randomised to placebo and the test product was not associated with more severe oral pain than placebo.

Results of the OCA, which involved both a broad evaluation of the mouth (general OCA) and effects of drug administration at the injection site and procedural site (specific OCA), showed minor abnormalities. Only 1 subject treated with the test product had a clinically significant OCA at any time point. This subject treated with the test product experienced hyperaemia at the primary injection site, which had resolved by 3 hours after study drug administration. The subject did not report using analgesic for this abnormal OCA finding.

Overall, the frequency of subjects with analgesic use for intraoral pain was low and similar both within the 4-hour observation period and within 24 hours after discharge.

**Study Conclusion**

This Phase II study supports the safety of the test product in a purely paediatric population. It is reassuring that the study drug was well tolerated with no real difference in adverse event profiles between drug and placebo groups.

Although a secondary endpoint, the efficacy measures were encouraging also and would support efficacy in 6-11 year olds. Therefore the lower age limit of 6 years in the SmPC is satisfactory.

**Phase III Studies**

The selection of the dose of phentolamine to be evaluated in the Phase III studies was based on the efficacy and safety results observed in the Phase I and II studies.

**Phase III Study 1**

This was a Phase III, multicentre, randomised, blinded, controlled clinical study designed to evaluate the efficacy, pharmacodynamics, and safety of the test product used for reversal of soft tissue anaesthesia (STA) in subjects undergoing restorative or periodontal maintenance procedures in the mandible. Procedures must have required local anaesthesia with an anaesthetic agent containing a vasoconstrictor.

Eligible subjects were randomised with respect to both the type of anaesthetic/vasoconstrictor and study drug (the test product or sham). Randomisation to local anaesthetic was performed prior to the start of the dental procedure and used a 2:1 ratio for 2% lidocaine/epinephrine versus another anaesthetic/vasoconstrictor combination. Other anaesthetics/vasoconstrictors were 4% articaine/epinephrine, 4% prilocaine/epinephrine, and 2% mepivacaine/levonordefrin. Each was randomly assigned using a 1:1:1 allocation ratio, resulting in a 6:1:1:1 overall ratio. Subjects could receive either 1 or 2 injections of anaesthetic, as deemed appropriate by the investigator for the dental procedure being
performed. The subject and the member of the investigative team who observed STA recovery and performed safety assessments were blinded to the treatment received.

Eighteen study centres enrolled subjects. Of the 244 subjects randomised to local anaesthetic, 163 were assigned to lidocaine/epinephrine and 81 were assigned to articaine/epinephrine, prilocaine/epinephrine, or mepivacaine/levonordefrin, as predicted by the overall randomisation ratio of 6:1:1:1 for the 4 anaesthetics, respectively.

A total of 120 males and 124 females were enrolled, ranging from 12 to ≥65 years of age. The treatment groups were comparable with respect to the numbers of subjects in each age group. All subjects completed the study.

Subjects were randomised to receive the test product or control in a 1:1 allocation ratio. This randomisation was stratified according to study centre, anaesthetic (lidocaine, other), the number of injections of anaesthetic administered (1 or 2), and subject age (12-17 years, 18-64 years and 65 years or older). Supplemental buccal or lingual infiltrations of the same anaesthetic were permitted as long as they were not likely to result in anaesthesia of the lip and/or tongue and comprised a volume less than 0.9 mL. Fifty-nine subjects (24.2%; 30 randomised to the test product; 29 randomised to placebo) required supplemental injections of anaesthetic. These supplemental injections comprised up to one-half cartridge (0.9 mL) given as buccal or sublingual infiltrations.

The anaesthetic was required to be administered by one of the following techniques:

1) inferior alveolar nerve block
2) Gow-Gates nerve block
3) Vazirani-Akinosi block
4) mental-incisive block
5) supraperiosteal injection.

The dental procedure had to be completed within 60 minutes of the first administration of local anaesthetic.

The number of cartridges of the test product or placebo injections was planned to be equal to the number of cartridges of anaesthetic. Deviations in either the number of cartridges of anaesthetic or study drug administered occurred during the treatment of 10 subjects (6 randomised to the test product and 4 randomised to sham), causing 6 of these subjects received a different number of cartridges of anaesthetic and study drug. As a result, the data sets for the efficacy and safety analyses had different distributions based on number of cartridges: the categorization of subjects for the primary efficacy analysis was based on number of cartridges of local anaesthetic, as prescribed in the protocol and SAP for an ITT analysis; the categorization of subjects for the safety analysis was based on the number of cartridges of study drug.

Study drug was administered at the same site(s) as the local anaesthetic by the same investigator who administered local anaesthetic.

One of three procedures was performed: cavity; crown or periodontal maintenance. At the completion of the dental procedure and assessments, the test product was administered in the same location as the primary injection of local anaesthetic, and if required, in the same location as the secondary injection of local anaesthetic. The test product was administered
using the same intraoral injection technique(s) as used for local anaesthetic administration. Sham injections were to mimic the time, preparation and application of the test product, through the use of a syringe with a capped needle that did not allow tissue penetration.

The primary efficacy variable was the time to recovery of normal sensation in the lower lip as measured by standardized palpation by subjects. Secondary assessments included the observed soft tissue sensation in the lower lip and tongue, perception of function/sensation (soft tissue anaesthesia recovery - STAR-7 questionnaire), observed functions of smiling, speaking, drinking and drooling (FAB).

The following sequence was used for efficacy assessments:

1) lip and tongue palpation
2) STAR questionnaire
3) functional assessment battery (FAB).

When a time point did not require the STAR assessment, the lip and tongue sensation ratings were to be done first, followed by the FAB. As there was no pre-existing patient reported outcome instrument designed to quantify a patient’s perceived clinical benefit of reversal of STA for this specific clinical situation, Novalar developed and validated a new instrument, the STAR Questionnaire. The STAR scoring in this study was based on 7 of the 12 questions (STAR-7; questions #2 [uncomfortable], 3 [biting], 4 [drinking], 6 [speaking], 7 [smiling], 8 [drooling], 11 [appearance to others]), which was to be self administered every 30 minutes during the 5-hour observation period after administration of study drug.

The primary endpoint analysis used the ITT efficacy data set and comprised all 244 randomised subjects, as specified in the protocol. The median elapsed time between injections of anaesthetic and study drug was 46 minutes (range: 17 to 78 minutes) for the overall cohort. Median elapsed times between anaesthetic and study drug were 47.5 minutes (range: 20 to 74 minutes) for subjects randomised to sham, and 44 minutes (range: 17 to 78 minutes) for subjects randomised to the test product.

A Kaplan-Meier survival analysis method was used to determine the median time to recovery of normal sensation in the lower lip. The analysis was adjusted for the type of anaesthetic and the number of cartridges used. No adjustment was made for study centre or age, despite these being stratification variables.

The decision to not analyse the results per centre or age group is justified as being due to the small number of patients recruited.

The median time to recovery of normal sensation was 70 minutes (95% confidence interval: 65 to 80 minutes) for subjects randomised to the test product and 155 minutes (95% confidence interval: 140 to 165 minutes) for subjects randomised to sham. The difference between these times was found to be highly significant ($p <0.0001$) using a log-rank test stratified for the number of cartridges and type of anaesthetic. The effect of the test product represented a reduction of 85 minutes (54.8%) in median time to recovery of normal lower lip sensation for subjects treated with the test product compared with placebo.
Please note that the test product on the graph is shown as NV-101.

The results per centre and per age group (not shown) demonstrate that there does not appear to be any evidence of a difference in efficacy between subgroups. In all centres bar one, the median effect of the test product is considerably stronger than that of placebo. The one centre where it was not had a small number of patients, and with so many centres, it is not surprising if one of them has results like this. Therefore it can be concluded that there is no evidence for a difference across subgroups used in the randomisation.

Further Kaplan-Meier analyses of the subsets of patients demonstrated that the ability of the test product to shorten the time required for recovery of normal sensation in the lower lip was observed for subjects treated with either 1 or 2 cartridges/control injections, for subjects in all 3 age groups, for subjects treated with either inferior alveolar block or mental-incisive block, for subjects undergoing cavity preparation/restoration/filling or periodontal maintenance, and for both males and females. The effect of the test product appeared to be consistent across all of the subgroups analysed, with the reduction factors ranging from 37.3% to 68.2%. The results per centre are shown below:
Significant reductions for the test product versus placebo also were observed for all secondary endpoints: time to perceived normal sensation and function (STAR-7 score of zero), time to observed recovery of normal function (normal FAB), and time to recovery of normal sensation in the tongue (p < 0.0001 for all comparisons).

The safety and tolerability of the test product was evaluated based on the following parameters:

- Incidence, severity, and duration of intraoral pain as measured by the H-P VAS
- Clinically significant findings from OCAs
- Analgesic requirements for the treatment of intraoral pain
- Changes in vital signs (blood pressure, pulse, respiration, and temperature)
- Incidence, severity, and duration of adverse events.

No serious adverse events were reported. Of the 77 adverse events, the majority (55 in 44 subjects) were deemed related to study drug: 32 adverse events in 24 subjects were related to the test product and 23 adverse events in 20 subjects were related to control. The most frequently reported treatment-related adverse events were injection site pain (15 subjects: the test product, 8; placebo, 7), post-procedural pain (14 subjects: the test product, 6; placebo, 8), headaches (6 subjects: the test product, 4; placebo, 2), hypertension (4 subjects: the test product, 2; sham 2), and post-procedural discomfort (3 subjects: the test product, 2; placebo, 1). All events were mild or moderate in severity. The frequency of adverse events was similar for subjects treated with 2 versus 1 cartridge. No relationship was apparent between the types of adverse events and age group.

Both a statistically and clinically significant effect was seen in the reduction in time to return to normal sensation. This was independent of type of local anaesthesia and technique; type of
procedure or any demographic feature. The frequency of adverse events was similar between groups also.

**Phase III Study 2**

This was a Phase III, multicentre, randomised, blinded, controlled clinical study designed to evaluate the efficacy, pharmacodynamics, and safety of the test product when used for reversal of soft tissue anesthesia (STA) in subjects undergoing restorative or periodontal maintenance procedures in the maxilla.

This study was of the same design as Phase III Study 1, above, except that the dental procedures were to the maxilla, as opposed to the mandible. The type of local anaesthetics used were the same as before, with the same randomisation (2:1 in favour of the most commonly used dental anaesthetic: lidocaine with epinephrine, resulting in a 6:1:1:1 ratio): 2% lidocaine with 1:100,000 epinephrine, 4% articaine with 1:100,000 epinephrine, 4% prilocaine with 1:200,000 epinephrine, or 2% mepivacaine with 1:20,000 levonordefrin. The following intraoral nerve blocks were permitted:

1) supraperiosteal injection
2) superior anterior alveolar nerve block
3) infraorbital nerve block.

The dental procedures were either restorative (cavity preparation, filling or crown) or maintenance (cleaning; non-surgical scaling; root planing).

Sixteen study centres enrolled subjects, 240 of whom were randomised. These comprised 11 males and 129 females aged 12 – 81 years. Of the 240 subjects randomised to local anaesthetic, 159 were assigned to lidocaine/epinephrine and 81 were assigned to articaine/epinephrine, prilocaine/epinephrine, or mepivacaine/levonordefrin, as predicted by the overall randomisation ratio of 6:1:1:1 for the 4 anaesthetics, respectively.

Thereafter, subjects were randomised to receive the test product or sham (control) in a 1:1 allocation ratio. This randomisation was stratified according to study centre, anaesthetic (lidocaine, other), the number of cartridges of anaesthetic administered (1 or 2), and subject age (12 to 17 years, 18 to 64 years, ≥ 65 years). Subjects who received 1 cartridge of anaesthetic were to receive 1 cartridge of the test product (0.4 mg phenolamine mesilate) or 1 placebo injection. Subjects who required 2 cartridges to achieve adequate pulpal anaesthesia were to receive 2 injections of the test product (total dose of 0.8 mg phenolamine mesilate) or 2 placebo injections.

Supplemental buccal or palatal infiltrations of the same anaesthetic were permitted in this study as long as they were not likely to result in STA of the upper lip and comprised a volume less than 0.9 mL. No test product was administered at sites of injection of supplemental anaesthetic.

As before, the primary efficacy endpoint was time to normal sensation of the upper lip as measured by standardized palpation by subjects. Secondary efficacy endpoints included the time to STAR-7 score of zero as measured with the STAR questionnaire, and the time to normal function as measured by the FAB. The primary endpoint analysis used the ITT analysis data set and comprised all 240 randomised subjects, as specified in the protocol.
The median elapsed time between injections of anaesthetic and study drug was 46.5 minutes (range: 13 to 83 minutes) for the overall cohort. Median elapsed times between anaesthetic and study drug were 45 minutes (range: 14 to 81 minutes) for subjects randomised to the test product and 47 (range: 13 to 83 minutes) for subjects randomised to sham.

A Kaplan-Meier survival analysis method was used to determine the median time to recovery of normal sensation in the upper lip. In the test product treatment group, all subjects achieved normal sensation in the upper lip by the end of the 5-hour observation period; therefore, none were censored. In the placebo group, 1 subject failed to achieve normal sensation in the upper lip by the end of the 5-hour observation period and was censored in the analysis.

The median time to recovery of normal sensation in the upper lip was 50 minutes (95% confidence interval: 45 to 60 minutes) for subjects randomised to the test product and 132.5 minutes (95% confidence interval: 115 to 145 minutes) for subjects randomised to placebo. The difference between these times was found to be highly significant (p < 0.0001) using a log-rank test stratified for the number of cartridges and type of anaesthetic. The effect of the test product represented a reduction of 82.5 minutes (62.3%) in median time to recovery of normal upper lip sensation for subjects treated with the test product compared with placebo:

Kaplan-Meier analyses of these subsets demonstrated that the ability of the test product to shorten the time required for recovery of normal sensation in the upper lip was observed for subjects treated with either 1 or 2 cartridges/placebo injections; for subjects in all 3 age groups; for subjects treated with superior anterior alveolar block, infraorbital nerve block or supraperiosteal injection; for subjects undergoing cavity preparation/restoration/filling or periodontal maintenance; and for both males and females. The effect of the test product appeared to be consistent across all but 1 of the subgroups analysed, with reduction factors...
ranging from 22.6% to 71.4%. The subgroup with inconsistent results comprised subjects treated with prilocaine as the anaesthetic (0% reduction factor). No explanation for this finding was suggested.

Significant reductions for the test product versus sham also were observed for time to perceived normal sensation and function (STAR-7 score of zero; \( p < 0.0001 \)) and time to observed recovery of normal function (normal FAB; \( p < 0.0001 \)).

Thirteen percent of subjects treated with the test product and 10% of subjects treated by placebo injection experienced treatment related, transient adverse events of mild to moderate severity, all of which resolved within the study period. No clinically significant changes in pain or vital signs were attributable to the test product. The most frequent study drug-related events (injection site pain, post-procedural pain and headaches) occurred in 4.2%, 2.1%, and 1.3% of all subjects, respectively. Frequencies of injection site pain, post-procedural pain, and headaches were similar in both treatment groups (test product: 6.7%, 1.7%, and 1.7%; placebo: 1.7%, 2.5%, and 0.8%, respectively). No relationship was apparent between the types of adverse events and age group.

As with the mandibular study, both a statistically and clinically significant effect was seen in the reduction in time to return to normal sensation. This was independent of type of local anaesthesia and technique; type of procedure or any demographic feature.

The study drug was well tolerated and few adverse events were recorded, with no particular differences between test and placebo.

The same stratification issues regarding the design and analysis were present for this trial. Again, there was no difference between age groups or centres, and the results can be considered robust. The need to account for the time between anaesthesia and receiving randomised treatment is also an additional concern with this trial.

**Analysis of Pivotal Studies Phase III Study 1 and 2 and Phase II Study 2**

**Introduction**

The Cox Proportional Hazards model was employed to analyse the effect of the two treatment groups and the possible effect of longer time between anesthesia and receiving study drug. The model included the fixed effects of: 1) treatment groups, and 2) length of time between anaesthetic to study drug administration. In addition, a single effect (unadjusted) model that included only the length of time between anaesthetic to study drug administration was also conducted. These models were run on the three pivotal studies (Phase III Study 1 and 2 and Phase II Study 2).

The result of these analyses is presented below.

**Full Cox proportional hazards model**

The consistency of treatment across strata was first evaluated by testing for the presence of treatment group by strata interaction. In the full model, the treatments by strata interaction effect for all three pivotal studies were not statistically significant as shown by the treatment-by-length of time between anaesthetic to study drug (Phase III Study 1: \( p=0.6595 \); Phase III Study 2: \( p=0.3937 \); Phase II Study 2: \( p=0.1195 \)). This indicates that the effect on the test product is independent of the time between anaesthetic to study drug administration. Because this interaction effect was not statistically significant, the interaction term was
dropped from further Cox proportional hazards modeling and a fixed-effect model was subsequently employed.

**Fixed-effects only Cox proportional hazards model**
The final “fixed-effects” Cox proportional hazards model is shown in the table below. The hazard ratio for the treatment group in this model was 3.25, 3.04, and 4.79 (respectively for Phase III Study 1 and 2 and Phase II Study 2), indicating that after adjustment for length of time between anesthesia to study drug administration, subjects in the test product treatment group were at least 3 times as likely as subjects in the sham group to achieve normal lip sensation during the 5-hour observation period. The treatment effect for all three pivotal studies was statistically significant ($p < 0.0001$).

The lack of statistical significance for other fixed effect (length of time between anaesthetic to study drug administration) for the three studies (Phase III Study 1: $p=0.1038$; Phase III Study 2: $p=0.4327$; and Phase II Study 2: $p=0.5388$) indicated that there was no effect of time from anesthesia to study drug administration on time to recovery of normal lip sensation after adjusting for the treatment effect.

**Unadjusted single fixed effect Cox proportional hazards model**
One additional model was conducted for exploratory purposes. In this Cox Proportional Hazards model only the fixed effect of time from anaesthesia to study drug administration was included in the model. In this case, the effect of time from anaesthesia to study drug administration was also shown not to be statistically significant for the three studies (Phase III Study 1: $p=0.7741$; Phase III Study 2: $p=0.9628$; and Phase II Study 2: $p=0.0948$). This again indicated there was no effect of time from anaesthesia to study drug administration on the primary endpoint of time to recovery of normal lip sensation in an unadjusted model.

<table>
<thead>
<tr>
<th>Study</th>
<th>Variable</th>
<th>P-Value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III Study 1</td>
<td>Interaction (*)</td>
<td>0.6595</td>
<td>1.004 (0.986, 1.023)</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>&lt;0.0001</td>
<td>3.253 (2.478, 4.270)</td>
</tr>
<tr>
<td></td>
<td>Length of time between anaesthetic and study drug administration</td>
<td>0.1038</td>
<td>1.008 (0.998, 1.018)</td>
</tr>
<tr>
<td></td>
<td>Length of time between anaesthetic and study drug administration (Unadjusted model)</td>
<td>0.7741</td>
<td>1.001 (0.992, 1.011)</td>
</tr>
<tr>
<td>Phase III Study 2</td>
<td>Interaction (*)</td>
<td>0.3937</td>
<td>0.992 (0.974, 1.010)</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>&lt;0.0001</td>
<td>3.042 (3.324, 3.983)</td>
</tr>
<tr>
<td></td>
<td>Length of time between anaesthetic and study drug administration</td>
<td>0.4327</td>
<td>1.004 (0.995, 1.013)</td>
</tr>
<tr>
<td></td>
<td>Length of time between anaesthetic and study drug administration (Unadjusted model)</td>
<td>0.9628</td>
<td>1.004 (0.996, 1.013)</td>
</tr>
<tr>
<td>Phase II Study 2</td>
<td>Interaction (*)</td>
<td>0.1195</td>
<td>1.027 (0.993, 1.062)</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>&lt;0.0001</td>
<td>4.795 (2.876, 7.994)</td>
</tr>
<tr>
<td></td>
<td>Length of time between anaesthetic and study drug administration</td>
<td>0.5388</td>
<td>1.005 (0.989, 1.021)</td>
</tr>
<tr>
<td></td>
<td>Length of time between anaesthetic and study drug administration (Unadjusted model)</td>
<td>0.0948</td>
<td>1.013 (0.998, 1.029)</td>
</tr>
</tbody>
</table>

The unadjusted fixed-effect model was the most useful. It clearly shows there is no overall effect of the variable 'time until anaesthesia', with point estimates of effect of less than 1.01. Additionally, the results for the treatment effect remain highly significant and the point
estimates for treatment effect are large. Thus the analyses have shows that the treatment
effect does not depend on the time since anaesthesia.

**Efficacy Conclusion**

From the patient studies, both Phase II and Phase III, the test product can be seen to have a
significant impact in the reduction of the time taken to regain normal sensation following
intraoral mucosal local anaesthetic injection with a vasoconstrictor. This effect would appear
consistent across four commonly used local anaesthetics, and independent of anaesthetic
technique; type of procedure or any demographic feature.

The time taken to return to normal sensation is, in effect, a surrogate for the functional
element associated with dental anaesthesia. This was evidenced in the correlation between
the return to sensation primary endpoint measure and the functional assessment battery. The
applicant states that prolonged soft tissue anaesthesia may interfere with patients normal
daily activities in three domains: perceptual (perception of altered physical appearance and
diminished function), sensory (lack of sensation) and functional (diminished actual ability to
speak, eat, drink and control drooling). Furthermore, soft tissue anaesthesia can be associated
with accidental, self-inflicted and soft tissue injury. This is of particular concern in children
and people with mental disability.

The results regarding the clinical significance of a 50-70 minute reduction in the mean time
to return of normal sensation and, ergo, function were statistically significant. The benefit is
balanced by a low incidence of adverse events. As stated earlier, the vasodilatory effect of
phentolamine may have an impact of the adverse event profile with regard to the potential for
post-procedural bleeding. It is noted that there was no increased incidence of local
haemorrhage at the injection site or regional haemorrhage in the oral cavity in the subset of
subjects undergoing deep scaling and root planing (a procedure often associated with
periodontal haemorrhage). Additionally, there was no evidence of increased bleeding in the
few subjects enrolled in the clinical trials who were treated with warfarin.

The test product has not been studied after tooth extraction and other invasive procedures. As
this potential has not been examined in these studies, a restriction to that effect has been
placed in Section 4.4 of the SmPC.

**Safety**

**Patient Population Exposure**

A total of 9 clinical studies were conducted involving a total of 885 subjects; 497 (56%)
receiving the test product or commercially available phentolamine mesilate and 388 (44%)
receiving a sham injection or placebo.

Of these, there were 5 studies (Phase III Studies 1 and 2, Phase II Studies 1 and 2 and
Pharmacokinetic Study 2) involving a cohort of 777 dental subjects (test product, N = 418;
control, N = 359), comprising children age 3 to 11 years old (test product, N = 109; control,
N = 56), adolescents age 12 to 17 years old (test product, N = 45; control, N = 40), and adults
(test product, N = 264; control, N = 263) undergoing routine dental procedures.

A further 3 studies (Dose Ranging Studies 1, 2 and 3) involved 92 healthy adult subjects not
undergoing dental procedures.
Safety information was obtained from the clinical trial exposure which consisted of 869 subjects enrolled in 8 clinical trials (out of 9), of which 481 were administered a single intraoral submucosal injection of phentolamine.

Separate additional safety data for test product was obtained from 16 healthy adult subjects in a pharmacokinetic study (Pharmacokinetic Study 1). All 16 subjects enrolled in the Pharmacokinetic Study 1 were not included in the clinical trial exposure analysis because they had been administered repeated doses of phentolamine, both by intravenous and intraoral submucosal injection. Because this pattern of phentolamine exposure was distinctly different from the other 481 subjects who were administered a single intraoral submucosal injection of phentolamine, data from these 16 subjects were not included in the analysis.

An integrated analysis of safety was conducted in the 5 studies where dental subjects were enrolled, which comprised 418 subjects randomised to the test product and 359 subjects randomised to the control group (placebo or sham injection). In the test product group, 284 subjects (68%) were administered a dose of 0.4 mg, 83 (20%) received 0.2 mg, and 51 (12%) received 0.8 mg. Safety analysis consisted of evaluation of adverse events, oral pain assessment by the Heft-Parker visual analog scale, and OCAs by visual inspection.

Treatment-emergent adverse events (TEAEs), i.e., adverse events reported in the period subsequent to study drug (the test product or sham injection) administration, occurred with similar frequencies in subjects in the test product groups (117 subjects [28.0%] with 161 events) or in the control groups (96 subjects [26.7%] with 120 events). To qualify as ADR, a TEAE had to have been reported in at least two subjects randomised to the test product and had to have a frequency in any the test product dose-group or total the test product group greater than the control group by at least 0.2%.

The majority of these adverse events were mild and resolved at the end of the observation or follow-up period. There were 4 severe adverse events reported, 3 in control subjects (one case each of post-procedural pain, injection site pain and pallor), and 1 in the test product group (post-procedural pain). By percentage of subjects, the most frequently reported TEAEs were tachycardia/sinus tachycardia (test product, 5.2%; control, 7.5%), injection site pain (test product, 5.3%; control, 3.9%), post-procedural pain (test product, 6.0%; control, 6.4%), and headache (test product, 3.1%; control, 3.9%):
Please note that the test product on the table is shown as NV-101.

A similar integrated analysis was performed for the 63 healthy adult subjects who were exposed to phentolamine mesilate doses ranging from 0.02 mg to 0.4 mg and the 29 healthy adult subjects who were exposed to placebo injection. Treatment-emergent adverse events (phentolamine mesilate, 26 events; control, 7 events) occurred with similar frequencies in subjects treated with phentolamine mesilate (20 subjects [31.7%]) or control (7 subjects [24.1%]). The majority of these adverse events were mild and resolved at the end of the observation or follow-up period.

In dental subjects there was no apparent relationship between adverse event frequency and dose of the test product. The percentage of subjects who reported post-procedural pain and headache appeared to slightly increase with increasing dose of the test product. However, a similar proportion of control subjects experienced these adverse events compared to subjects treated with 0.4 mg of the test product, suggesting no real dose effect.

In healthy subjects there was no apparent relationship between adverse event frequency and dose of the test product. The 0.08 mg dose group had a higher overall frequency of adverse events, with no particular adverse event predominating.

Detailed analysis of the treatment-emergent adverse events by subgroups (age, gender, race) did not reveal any specific risk for the subpopulations studied.

In Pharmacokinetic Study 1, one dose group administered the test product at 0.4 mg IV was intended to model the accidental intravenous delivery of the test product. Subjects received 1 cartridge of the test product (0.4 mg in 1.7 ml) injected IV over one minute. No local anaesthetic was administered. The incidence of adverse events was not different than compared with the other treatment periods in this study. A total of 10 subjects experienced adverse events in this treatment period. Five subjects experienced hypotension defined as a systolic blood pressure of less than 100 mm Hg; all episodes were mild and asymptomatic. In 3 subjects, the event was deemed by the investigator related to study injection (the test product or anaesthetic). Two subjects experienced bradycardia; in 1 subject, the event was deemed by the investigator related to study injection. One subject each experienced the
following adverse events that were deemed unrelated to study injection: headache, severe injection site pain (pain above the IV site) and fatigue. There was no apparent relationship between adverse event frequency and dose of the test product. All adverse events resolved. Electrocardiogram (ECG) readings were performed for 12 of 16 subjects for treatment arm B, where the test product was administered IV and all of the results were normal.

These findings provide reassurance that there were no particular adverse events attributable to the test product in its intended use and the test product was not associated with adverse reactions that might be associated with the systemic use of phentolamine mesilate, such as hypotension or cardiovascular events, even when administered intravenously. There was no evidence of toxicity due to faster clearance of the local anaesthetic and/or the catecholamine vasoconstrictor in the systemic circulation following the test product administration either

**Additional data on post-procedural analgesic use due to a post-procedural pain and bleeding**

Post-procedural pain and analgesic use in the Phase III studies 1 and 2 specifically showed comparable incidence in the test product and control groups. The incidence of bleeding was low and comparable in the test product and control groups. More specifically, injection site haemorrhage was reported in 2 of 418 patients (0.5%) randomised to the test product and 2 of 389 patients (0.6%) randomised to control. No post-procedural bleeding was reported.

Patients underwent OCAs during the observation period to evaluate any local adverse reaction in the intraoral cavity (General OCA) and at the procedure site and injection site (Specific OCA). Any clinically significant finding was reported as adverse event. Four cases of haemorrhage (all described as mild) were reported in the Phase III Study 1 (3 cases in the test product group, 1 case in the Sham group). Of the three test product cases of haemorrhage, 2 had resolved after 15 minutes of drug administration, one was mild petechiae that were fading. No cases of haemorrhage were reported in the Phase III Study 2.

All patients underwent non-invasive dental procedures in these studies and there are no clinical data on the test product use in patients undergoing surgical or invasive dental procedures. Therefore the following statement has been included in Section 4.4. of the SmPC (Special warnings and precautions for use) “Use of OraVerse is not recommended in patients undergoing complex dental procedures where post-procedural pain and haemorrhage is anticipated”.

**Populations Not Studied in the Pre-Approval Phase**

**Paediatric population:** There are no data on the use of OraVerse 400 micrograms/1.7 ml solution for injection in patients less than 3 years of age and those weighing less than 15 kg. There is a limited set of safety data for patients 3 to 5 years old (only 21 patients exposed). Therefore, information on use in children under the age of 6 years or weighing less than 15 kg is considered to be missing.

Doses comprising more than 1 cartridge (400 micrograms) of OraVerse 400 micrograms/1.7 ml solution for injection have not been studied in children less than 12 years of age because a dose of local anaesthetic greater than one cartridge is usually not necessary for routine dental procedure in this age group.

The age range proposed to be authorised is adults and children aged 6 years and older.
Pregnancy and breast-feeding: Neither pregnant women, nor breast-feeding women were enrolled in any studies. Use in pregnant and nursing women is considered missing information.

Patients with hepatic impairment: OraVerse 400 micrograms/1.7 ml solution for injection has not been evaluated in patients with hepatic impairment. Phentolamine is metabolised principally in the liver. The SmPC (section 4.2) recommends caution when using OraVerse with in patients with hepatic impairment.

Patients with renal impairment: OraVerse 400 micrograms/1.7 ml solution for injection has not been evaluated in patients with renal impairment. Less than 10% of the administered dose is excreted unchanged in urine. Dose adjustment is not required in patients with renal impairment.

Patients with the following conditions were generally excluded from participation in clinical trials: unstable angina; uncontrolled cardiac arrhythmias; uncontrolled hypertension; hyperthyroidism; significant infection or inflammatory process of the oral cavity; pregnancy; and in the case of children, those whose weight was less than 15 kg.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are clinically satisfactory.

Clinical Overview
The clinical overview and summary have been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA Form
The MAA form is clinically satisfactory.

Conclusions
From the data presented, it can be concluded that OraVerse 400 micrograms/1.7 ml solution for injection significantly reduces the time taken to return to normal sensation following submucosal injection of a local anaesthetic with a catecholamine vasoconstrictor. This statistically significant reduction translates to a 50-70 minute reduction in the mean time to return of normal sensation. The clinical benefit is balanced by a low incidence of adverse events. There were no particular adverse events attributable to the test product in its intended use and the test product was not associated with adverse reactions that might be associated with the systemic use of phentolamine mesilate, such as hypotension or cardiovascular events, even when administered intravenously. There was no evidence of toxicity due to faster clearance of the local anaesthetic and/or the catecholamine vasoconstrictor in the systemic circulation following the test product administration either.

It is recommended that a Marketing Authorisation is granted for this application from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of OraVerse 400 micrograms/1.7 ml solution for injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

Regarding the non-clinical studies which were provided, the results of the blood-flow investigations support the postulated clinical mechanism of action. Additional safety pharmacology studies are not required, as observations on the cardiac and respiratory systems were included in the single- and repeat-dose toxicology studies presented. The duration of the toxicity studies with the proposed product and impurities is sufficient to support the application. There were no findings of toxicological concern in the single- or repeated-dose studies. The genotoxicity studies conducted on the degradants provides evidence that they are neither mutagenic nor clastogenic and it is accepted that they have been adequately qualified.

CLINICAL

From the data provided, it can be concluded that OraVerse 400 micrograms/1.7 ml solution for injection significantly reduces the time taken to return to normal sensation following submucosal injection of a local anaesthetic with a catecholamine vasoconstrictor. The clinical benefit is balanced by a low incidence of adverse events. There was no evidence of toxicity due to faster clearance of the local anaesthetic and/or the catecholamine vasoconstrictor in the systemic circulation following the test product administration either.

The SmPC, PIL and labelling are clinically satisfactory.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with phentolamine mesilate is considered to have demonstrated the therapeutic value of the compound. The risk benefit assessment is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>