HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KOVANAZE™ NASAL SPRAY safely and effectively. See full prescribing information for KOVANAZE NASAL SPRAY.

KOVANAZE (tetracaine HCl and oxymetazoline HCl) Nasal Spray
Initial U.S. Approval: 2016

INDICATIONS AND USAGE
KOVANAZE contains tetracaine HCl, an ester local anesthetic, and oxymetazoline HCl, a vasoconstrictor. KOVANAZE is indicated for regional anesthesia when performing a restorative procedure on Teeth 4-13 and A-J in adults and children who weigh 40 kg or more (1).

DOSAGE AND ADMINISTRATION
KOVANAZE is for intranasal use only (2). Administer KOVANAZE ipsilateral (on the same side) to the maxillary tooth on which the dental procedure will be performed.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 18 years old)</td>
<td>2 sprays (0.2 mL per spray), 4 to 5 minutes apart</td>
</tr>
<tr>
<td></td>
<td>1 additional spray (0.2 mL) if adequate anesthesia has not been achieved 10 minutes after the second spray</td>
</tr>
<tr>
<td>Children who weigh 40 kg or more</td>
<td>2 sprays (0.2 mL per spray), 4 to 5 minutes apart</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS
Known hypersensitivity to tetracaine, benzyl alcohol, other ester local anesthetics, ρ-aminobenzoic acid (PABA), oxymetazoline, or any other component of the product (4).

ADVERSE REACTIONS
The most common adverse reactions occurring in >10% of patients include rhinorrhea, nasal congestion, oropharyngeal pain, and lacrimation increased (6).

Drug Interactions
Monoamine oxidase inhibitors (MAOIs): Concomitant use of MAOIs, nonselective beta adrenergic antagonists, or tricyclic antidepressants may cause hypertension and is not recommended (7.1).

Methemoglobinemia: May cause methemoglobinemia, particularly with used with methemoglobin-inducing agents. Use in patients with history of congenital or idiopathic methemoglobinemia not advised. If central cyanosis unresponsive to oxygen therapy occurs, suspect methemoglobinemia, confirm diagnosis with CO-oximetry, and treat with a standard clinical regimen (5.4).

Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.5).

WARNINGS AND PRECAUTIONS
Hypertension and Thyroid Disease: Shown to increase blood pressure in some clinical trial patients. Monitor blood pressure. Use in patients with inadequately controlled hypertension or active thyroid disease is not advised (5.1).

Epistaxis: Use is not recommended in patients with a history of frequent nose bleeds (≥5 per month). If a decision to use is made, monitor these patients carefully (5.2).

Dysphagia: Carefully monitor patients for dysphagia (5.3).

Methemoglobinemia: May cause methemoglobinemia, particularly when used with methemoglobin-inducing agents. Use in patients with history of congenital or idiopathic methemoglobinemia not advised. If central cyanosis unresponsive to oxygen therapy occurs, suspect methemoglobinemia, confirm diagnosis with CO-oximetry, and treat with a standard clinical regimen (5.4).

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Drug Interactions
Monoamine oxidase inhibitors (MAOIs): Concomitant use of MAOIs, nonselective beta adrenergic antagonists, or tricyclic antidepressants may cause hypertension and is not recommended (7.1).

Oxymetazoline-containing products: Discontinue use 24 hours prior to KOVANAZE administration (7.2).

Intranasal products: Avoid concomitant use (7.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2016
2.3 Reactions (6.1)

In clinical trials, dysphagia occurred more frequently with KOVANAZE than placebo. Carefully monitor patients for this adverse reaction.

5.3 Dysphagia

In clinical trials, dysphagia occurred more frequently with KOVANAZE than placebo. Carefully monitor patients for this adverse reaction.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Important Dosage and Administration Instructions

- KOVANAZE is for intranasal use only.
- Administer ipsilateral (same side) to the maxillary tooth on which the dental procedure will be performed.
- Wait 10 minutes after administration of KOVANAZE to perform a test drill to confirm that the tooth involved is anesthetized. A patient may not experience the same sensations of numbness or tingling of the lips and cheeks associated with injectable anesthetics.

#### 2.2 Dosing in Adults (≥ 18 years old)

- 2 sprays (0.2 mL each) administered 4 to 5 minutes apart in the nostril ipsilateral to the maxillary tooth on which the dental procedure will be performed. Initiate the dental procedure 10 minutes after the second spray.
- 1 additional spray (0.2 mL) if adequate anesthesia to initiate the dental procedure has not been achieved 10 minutes after the second spray.

#### 2.3 Dosing in Children (who weigh 40 kg or more)

- 2 sprays (0.2 mL each) administered 4 to 5 minutes apart in the nostril ipsilateral to the maxillary tooth on which the dental procedure will be performed. Initiate the dental procedure 10 minutes after the second spray.

### 3 DOSAGE FORMS AND STRENGTHS

KOVANAZETM Nasal Spray is a pre-filled, single-use, intranasal sprayer containing a clear 0.2 mL aqueous solution at pH 6.0 ± 1.0 comprising 30 mg/mL of tetracaine hydrochloride and 0.5 mg/mL of oxymetazoline hydrochloride (equivalent to 26.4 mg/mL tetracaine and 0.44 mg/mL oxymetazoline).

Each nasal spray unit delivers one 0.2 mL spray.

Each 0.2 mL spray contains 6 mg tetracaine hydrochloride (equivalent to 5.27 mg tetracaine) and 0.1 mg oxymetazoline hydrochloride (equivalent to 0.088 mg oxymetazoline).

### 4 CONTRAINDICATIONS

KOVANAZETM is contraindicated in patients with a history of allergy to or intolerance of tetracaine, benzyl alcohol, other ester local anesthetics, p-aminobenzoic acid (PABA), oxymetazoline, or any other component of the product. [see Warnings and Precautions (5.5)].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Risk of Hypertension

KOVANAZETM has not been studied in Phase 3 trials in adult dental patients with blood pressure greater than 150/100 or in those with inadequately controlled active thyroid disease. KOVANAZETM has been shown to increase blood pressure in some patients in clinical trials. Monitor patients for increased blood pressure. Use in patients with uncontrolled hypertension or inadequately controlled active thyroid disease of any type is not advised [see Adverse Reactions (6.1)].

#### 5.2 Epistaxis

In clinical trials, epistaxis occurred more frequently with KOVANAZETM than placebo. Either do not use KOVANAZETM in patients with a history of frequent nose bleeds (≥ 5 per month) or monitor patients with frequent nose bleeds more carefully if KOVANAZETM is used. [see Adverse Reactions (6.1)].

#### 5.3 Dysphagia

In clinical trials, dysphagia occurred more frequently with KOVANAZETM than placebo. Carefully monitor patients for this adverse reaction.

### 6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Hypertension [see Warnings and Precautions (5.1)]
- Epistaxis [see Warnings and Precautions (5.2)]
- Dysphagia [see Warnings and Precautions (5.3)]
- Methemoglobinemia [see Warnings and Precautions (5.4)]
- Anaphylactic Reactions [see Warnings and Precautions (5.5)]

#### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The adverse reactions information described below is from Phase 3 randomized, controlled clinical trials [see Clinical Studies (14)]. These data reflect exposure to KOVANAZETM in 154 adult dental patients and 20 pediatric dental patients (aged 7 to 17 years) with a need for an operative restorative dental procedure requiring local anesthesia for a single vital maxillary tooth (other than a maxillary first, second, or third molar) with no evidence of pulpal pathology. [see Clinical Studies (14)].

Common Adverse Reactions in Adult Dental Patients and Pediatric Patients Weighing 40 kg or More

The most common adverse reactions to occur in Phase 3 trials with KOVANAZETM in adult dental patients and pediatric dental patients weighing 40 kg or more were rhinorrhea, nasal congestion, nasal discomfort, oropharyngeal pain, and laceration increased [Table 1].

No serious adverse events with KOVANAZETM have occurred [see Clinical Studies (14.1)].

<table>
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</tr>
</tbody>
</table>

**5.4 Methemoglobinemia**

Tetracaine may cause methemoglobinemia, particularly in conjunction with methemoglobin-inducing agents. Based on the literature, patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Use of KOVANAZETM in patients with a history of congenital or idiopathic methemoglobinemia is not advised.

Patients taking concomitant drugs associated with drug-induced methemoglobinemia, such as sulfonamides, acetaminophen, acetylaminophen, anilines, dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrates, nitrofurantoin, nitroglycerin, nitroprusside, pamidronate, p-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, and quinine, may be at greater risk for developing methemoglobinemia.

Initial signs and symptoms of methemoglobinemia (which may be delayed for up to several hours following exposure) are characterized by a slate grey cyanosis seen in, e.g., buccal mucous membranes, lips and nail beds. In severe cases, symptoms may include central cyanosis, headache, lethargy, dizziness, fatigue, syncope, dyspnea, CNS depression, seizures, dysrhythmia and shock. Methemoglobinemia should be considered if central cyanosis unresponsive to oxygen therapy occurs, especially if methemoglobinemia-inducing agents have been used. Calculated oxygen saturation and pulse oximetry are inaccurate in the identification of methemoglobinemia. Confirm diagnosis by measuring methemoglobin level with co-oximetry. Normally, methemoglobinemia levels are <1%, and cyanosis may not be evident until a level of at least 10% is present.

Treat clinically significant symptoms of methemoglobinemia with a standard clinical regimen such as a slow intravenous infusion of methylene blue at a dosage of 1-2 mg/kg given over a 5 minute period.

#### 5.5 Anaphylactic Reactions

Allergic or anaphylactic reactions have been associated with tetracaine, and may occur with other components of KOVANAZETM. They are characterized by urticaria, angioedema, bronchospasm, and shock. If an allergic reaction occurs, seek emergency help immediately.
with KOVANAZE. Concomitantly administered intranasal products. Do not administer other intranasal products with KOVANAZE.

Oxymetazoline has been known to slow the rate, but not affect the extent of absorption of concomitantly administered intranasal products. Do not administer other intranasal products with KOVANAZE.

7.3 Intranasal Products

Oxymetazoline has been known to slow the rate, but not affect the extent of absorption of concomitantly administered intranasal products. Do not administer other intranasal products with KOVANAZE.

Table 1: Common Adverse Reactions in ≥ 2% of Phase 3 Adult Dental Patients and Pediatric Patients Weighing 40 kg or More

<table>
<thead>
<tr>
<th>SOC / Preferred Term</th>
<th>KOVANAZE (N=174)</th>
<th>Active Comparator* (N=54)</th>
<th>Placebo (N=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory System Disorders</strong></td>
<td>141 (81%)</td>
<td>50 (93%)</td>
<td>18 (21%)</td>
</tr>
<tr>
<td>Rhinorrhea (runny nose)</td>
<td>91 (52%)</td>
<td>20 (37%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>56 (32%)</td>
<td>34 (63%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Nasal discomfort</td>
<td>45 (26%)</td>
<td>7 (13%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Oropharyngeal pain (sore throat)</td>
<td>25 (14%)</td>
<td>5 (9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Intranasal hypoesthesia</td>
<td>16 (10%)</td>
<td>8 (15%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Pharyngeal hypoesthesia (numb throat)</td>
<td>17 (10%)</td>
<td>10 (19%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Throat Irritation</td>
<td>15 (9%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>39 (22%)</td>
<td>5 (9%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Headache</td>
<td>18 (10%)</td>
<td>3 (6%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14 (8%)</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Sinus headache</td>
<td>5 (3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>16 (9%)</td>
<td>5 (9%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Oral Discomfort</td>
<td>4 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>12 (7%)</td>
<td>0 (0%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>BP systolic increased</td>
<td>8 (5%)</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>BP diastolic increased</td>
<td>6 (3%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td>8 (5%)</td>
<td>5 (9%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>5 (3%)</td>
<td>3 (6%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>6 (3%)</td>
<td>2 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (3%)</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

* Active Comparator was tetracaine only spray used in two clinical studies in adults.

Intranasal ulcerations, some of which were transient, were noted to have occurred following treatment with KOVANAZE. In Phase 3 trials, 6 (3%) patients who received KOVANAZE, but no patients who received placebo, developed nasal ulcers that were present on exam the same day as KOVANAZE dosing. Three (2%) KOVANAZE and 2 (2%) placebo-treated patients without nasal ulcerations on the day of KOVANAZE or placebo dosing were observed to have nasal ulcerations at the next day follow-up visit.

Less Common Adverse Reactions in Phase 3 Clinical Trials Adult Dental Patients and Pediatric Dental Patients Weighing 40 kg or More

Dysphagia (i.e., the sensation of difficult swallowing) is a notable adverse reaction reported in patients who received placebo. Other reported adverse reactions at 1% or more in any of the treatment groups included headache, rhinorrhea, runny nose, nasal congestion, sneezing, nasal dryness, sinus headache, dizziness, epistaxis, throat irritation, nasopharyngeal pain, and nasal irritation.

7.4 Drugs That May Cause Methemoglobinemia When Used with KOVANAZE

Tetracaine may cause methemoglobinemia, particularly in conjunction with methemoglobin-inducing agents such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrates, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, p-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaparine, and quinine. Monitor patients carefully for signs of methemoglobinemia if KOVANAZE is used in the setting of these drugs. [See Warnings and Precautions 5.4]

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data on tetracaine use in pregnant women are not sufficient to inform any risks. Published epidemiologic studies of nasal oxymetazoline used as a decongestant during pregnancy do not identify a consistent association with any specific malformation or pattern of malformations [see Data]. In animal reproduction and development studies, oxymetazoline given subcutaneously to rats caused embryo-fetal toxicity manifested by reduced implantation sites and live litter sizes at approximate 1.5 times the MRHD, and increased pup mortality at 6 times the MRHD. No adverse developmental effects were observed following subcutaneous administration of tetracaine HCI only to rats and rabbits during organogenesis at 32 and 6 times, respectively, the estimated exposure of tetracaine HCI at the 18 mg MRHD of KOVANAZE [see Data].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Published epidemiologic studies of nasal oxymetazoline used as a decongestant during pregnancy do not identify a consistent association with any specific malformation or pattern of malformations. These data are limited by the small number of cases exposed, multiple comparisons which may have resulted in chance findings, and analyses based on decongestants as a group.

Animal Data

In an embryo-fetal development study, pregnant rats were administered subcutaneous doses of oxymetazoline HCl only at 0.1 mg/kg, tetracaine HCI only at 7.5 mg/kg, or oxymetazoline HCl at 0.01, 0.03, 0.01, and 0.01 mg/kg/day in combination with 7.5 mg/kg tetracaine HCl during the pregnancy and lactation period. Oxymetazoline HCl treatment at 0.1 mg/kg/day (7.6 times the oxymetazoline AUC exposure at the maximum recommended human dose [MRHD] of KOVANAZE [3 mg oxymetazoline HCl and 18 mg tetracaine HCl]) caused reduced fetal weight and structural abnormalities including external and skeletal malformations (e.g., short forelimb digits, fused arches in thoracic vertebrae, fused ribs, and irregular number of ribs), and variations (e.g., irregularly shaped arches and increased bidual centra in thoracic vertebrae, and un-osified forelimb phalans) in the presence of maternal toxicity (reduced food consumption, body weight gain, and absolute body weight). However, the structural abnormality findings cannot be clearly attributed to the maternal toxicity. Adverse developmental effects were not observed when pregnant rats were co-administered the same dose of oxymetazoline HCl in combination with 7.5 mg/kg/day tetracaine HCI, or with 7.5 mg/kg/day tetracaine HCI alone. The no-observed-adverse-effect-level (NOAEL) for fetal effects was 0.03 mg/kg/day oxymetazoline HCl (1.5 times the oxymetazoline AUC exposure at the MRHD) and 7.5 mg/kg/day tetracaine HCl (30 times the AUC exposure as measured by PBBA [major tetracaine metabolite] at the MRHD).

In other embryo-fetal development studies, tetracaine base alone administered subcutaneously did not cause structural abnormalities in rats at doses up to 10 mg/kg/day (approximately 6.1 times the MRHD level of 18 mg tetracaine HCI by body surface area (BSA) comparison) or in rabbits at subcutaneous doses up to 5 mg/kg/day (approximately 6.1 times the MRHD level by BSA comparison).

In a prenatal and postnatal development study, pregnant rats were given subcutaneous doses of oxymetazoline HCl only at 0.1 mg/kg/day, tetracaine HCI only at 7.5 mg/kg/day, and oxymetazoline HCl at 0.01, 0.03, and 0.01 mg/kg/day in combination with 7.5 mg/kg/day tetracaine HCI from GD 7 to Lactation Day [LD] 20 (corresponding to the beginning of organogenesis through parturition and subsequent pup weaning). Oxymetazoline HCI treatment decreased the mean number of implant sites/litter at ≥ 0.03 mg/kg (≥ 1.5 times the oxymetazoline AUC exposure at the MRHD) when administered alone (19%) and co-administered with 7.5 mg/kg/day tetracaine HCI at 0.01, 0.03, and 0.1 mg/kg/day in combination with 7.5 mg/kg/day tetracaine HCI during the pregnancy and lactation period. Oxymetazoline HCl treatment significantly decreased at 0.1 mg/kg oxymetazoline HCl (6 times the oxymetazoline AUC exposure at the MRHD) when administered alone (19%) and co-administered with 7.5 mg/kg/day tetracaine HCI (11%). In addition, a decrease in pup survival was observed at the 0.17/5 mg/kg oxymetazoline HCI/tetracaineHCI dose (91.9%) compared to the control (99.6%), but no effects in any other groups. Maternal toxicity (e.g., mortality and reduced body weight gain, absolute body weight and food consumption) occurred in groups administered 0.1 mg/kg/day oxymetazoline HCl; however, the adverse developmental changes observed at this dose cannot clearly be attributed to the maternal toxicity. There were no adverse effects on sexual maturation, neurobehavioral, or reproductive function in the offspring at any maternal...
dose. The no-effect level for oxymetazoline HCl for maternal reproduction was 0.01 mg/kg/day (0.5 times oxymetazoline AUC exposure at the MRHD) and for pup growth and development was 0.03 mg/kg/day (1.5 times oxymetazoline AUC exposure at the MRHD). The no-effect level for tetracaine HCl for maternal reproduction and pup growth and development was 7.5 mg/kg/day (12 times the AUC exposure as measured by PBBA at the MRHD).

8.2 Lactation

Risk Summary

There are no data on the presence of tetracaine, oxymetazoline, or their metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Detectable levels of oxymetazoline, tetracaine and the major metabolite of tetracaine, p-butylnaminobenzoic acid (PBBA), were found in the milk of lactating rats following subcutaneous administration of oxymetazoline HCl in combination with tetracaine HCl during the period of organogenesis through parturition and subsequent pup weaning [see Data]. Due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for KOVANAZE and any potential adverse effects on the breastfed infant from KOVANAZE or from the underlying maternal condition.

Data

In a pre- and post-natal development study, rats were given oxymetazoline HCl subcutaneously at doses of 0.01, 0.03, and 0.1 mg/kg/day (0.6, 1.5, and 7.6 times, respectively, the oxymetazoline AUC exposure at the MRHD) in combination with 7.5 mg/kg tetracaine HCl (12 times the AUC exposure as measured by PBBA at the MRHD) from Gestational Day (GD) 7 to Lactation Day (LD) 20. Concentrations of oxymetazoline, tetracaine, and PBBA were measured in the milk of lactating rats at approximately 2 hours postdose on LD 15. The concentrations of oxymetazoline were generally dose dependent (2.5, 7.0, and 33.8 ng/mL at 0.01, 0.03, and 0.1 mg/kg/day, respectively). The concentrations of tetracaine and PBBA were generally similar across all 7.5 mg/kg/day tetracaine HCl dosing groups regardless of the presence of oxymetazoline (54.2 – 72.9 ng/mL for tetracaine, and 100.5 – 131.2 ng/mL for PBBA).

8.3 Females and Males of Reproductive Potential

Infertility

Based on animal data, KOVANAZE may reduce fertility in females of reproductive potential. In female rats, decreased fertility noted as a decrease in litter size occurred at 0.7 times the oxymetazoline AUC exposure at the MRHD of KOVANAZE. It is not known if the effects on fertility are reversible [see Nonclinical Toxicology (13.1)].

Males

Based on animal data, KOVANAZE may reduce male fertility. In male rats, decreased sperm motility and sperm concentration occurred at approximately 2 times the oxymetazoline AUC exposure at the MRHD of KOVANAZE [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

KOVANAZE has not been studied in pediatric patients under 3 years of age and is not advised for use in pediatric patients weighing less than 40 kg because efficacy has not been demonstrated in these patients [see Clinical Studies (14.2)].

8.5 Geriatric Use

Clinical studies of KOVANAZE did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Monitor geriatric patients for signs of local anesthetic toxicity, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other agents.

Experience has not identified differences in responses between the elderly and younger patients. Monitor geriatric patients for signs of local anesthetic toxicity.

8.6 Hepatic Disease

Because of an inability to metabolize local anesthetics, those patients with severe hepatic disease may be at a greater risk of developing toxic plasma concentrations of tetracaine. Monitor patients with hepatic disease for signs of local anesthetic toxicity.

8.7 Pseudocholinesterase Deficiency

Because of an inability to metabolize local anesthetics, those patients with pseudocholinesterase deficiency may be at a greater risk of developing toxic plasma concentrations of tetracaine. Monitor patients with pseudocholinesterase deficiency for signs of local anesthetic toxicity.

10 OVERDOSAGE

No addictive properties have been reported in the literature for either tetracaine or oxymetazoline, but there have been numerous case reports of unintended overdose for both compounds. Side effects in adults and children associated with oxymetazoline overdose include dizziness, chest pain, headaches, myocardial infarction, stroke, visual disturbances, arrhythmia, hypertension, or hypotension. Side effects of tetracaine overdose include rapid circulatory collapse, cardiac arrest, and cerebral events.

Possible rebound nasal congestion, irritation of nasal mucosa, and adverse systemic effects (particularly in children), including serious cardiac events, have been associated with overdosage and/or prolonged or too frequent intranasal use of oxymetazoline containing agents.

Accidental ingestion of imidazoline derivatives (i.e., oxymetazoline, naphazoline, tetrahydrozoline) in children has resulted in serious adverse events requiring hospitalization (e.g., coma, bradycardia, decreased respiration, sedation, and somnolence).

Patients should be instructed to avoid using oxymetazoline-containing products (such as Afrin®) and other α-adrenergic agonists within 24 hours prior to their scheduled dental procedure [see Drug Interactions (7.2)].

Management of an overdose includes close monitoring, supportive care, and symptomatic treatment.

11 DESCRIPTION

KOVANAZE (tetracaine HCl and oxymetazoline HCl) Nasal Spray is a clear aqueous solution in a pre-filled, single-use intranasal sprayer. The solution pH is 6.0 ± 1.0. The product contains two active ingredients: 30 mg/mL tetracaine HCl (equivalent to 26.4 mg/mL tetracaine) and 0.5 mg/mL oxymetazoline hydrochloride (equivalent to 0.44 mg/mL oxymetazoline). Each spray delivers 0.2 mL of solution containing 6 mg tetracaine hydrochloride (equivalent to 5.27 mg tetracaine) and 0.1 mg of oxymetazoline hydrochloride (equivalent to 0.088 mg oxymetazoline). The product also contains citric acid, sodium citrate, hydroxyethylcellulose, benzyl alcohol, and water. Sodium hydroxide and/or hydrochloric acid are added for pH adjustment as needed.

Tetracaine hydrochloride is an ester local anesthetic. Chemically it is 2-(dimethylamino)ethyl 4-(butylamino)benzoate hydrochloride. Its molecular weight is 300.8 for the hydrochloride salt and 264.4 for the free base. It is freely soluble in water and soluble in ethanol. Its structural formula is:

Oxymetazoline hydrochloride is a vasoconstrictor. Chemically it is 3-[(4,5-dihydro-1H-imidazol-2-yl)(methyl)-6-(1,1, dimethylethyl)-2,4-dimethylphenol mono-hydrochloride. Its molecular weight is 296.8 for the hydrochloride salt and 260.4 for the free base. It is freely soluble in water and ethanol and has a partition coefficient of 0.1 in octanol/water. Its structural formula is:

H₃C

α

2-

H₂C

O

O

N

H

HCl

HCl

HCl

HCl

HCl

HCl

HCl

Oxymetazoline hydrochloride is a vasoconstrictor. Chemically it is 3-[(4,5-dihydro-1H-imidazol-2-yl)(methyl)-6-(1,1, dimethylethyl)-2,4-dimethylphenol mono-hydrochloride. Its molecular weight is 296.8 for the hydrochloride salt and 260.4 for the free base. It is freely soluble in water and ethanol and has a partition coefficient of 0.1 in octanol/water. Its structural formula is:

H₃C

α

2-

H₂C

O

O

N

H

HCl

HCl

HCl

HCl

HCl

HCl

HCl

Oxymetazoline hydrochloride is a vasoconstrictor. Chemically it is 3-[(4,5-dihydro-1H-imidazol-2-yl)(methyl)-6-(1,1, dimethylethyl)-2,4-dimethylphenol mono-hydrochloride. Its molecular weight is 296.8 for the hydrochloride salt and 260.4 for the free base. It is freely soluble in water and ethanol and has a partition coefficient of 0.1 in octanol/water. Its structural formula is:

H₃C

α

2-

H₂C

O

O

N

H

HCl

HCl

HCl

HCl

HCl

HCl

HCl

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AUC exposures equivalent to 0.7 times the MRHD and higher, given alone or in combination with tetracaine HCl. Reduced numbers of corpora lutea and implantation sites were observed at 7.5 times the oxymetazoline AUC exposure at the MRHD in animals given oxymetazoline HCl alone or in combination with tetracaine HCl. These effects were attributed to oxymetazoline HCl because similar effects were not observed in rats given tetracaine HCl alone. A no-effect level for fertility in female rats was not established in this study.

No effects on male or female fertility were attributed to tetracaine HCl at 7.5 mg/kg/day (28 and 33 times the AUC exposure for males and females, respectively, as measured by PBBA [major tetracaine metabolite]) at the MRHD of KOVANAZE.

14 CLINICAL STUDIES

The efficacy of KOVANAZE Nasal Spray for regional anesthesia when performing a restorative procedure on Teeth 4-13 and A-J has been evaluated in three adult dental patient studies, as well as one pediatric dental patient study. The primary endpoint for all four studies was the successful completion of a restorative operative dental procedure without the need for a rescue injection. One adult dental study was terminated early for reasons related to the administration of KOVANAZE. Unlike the other studies conducted, in this study all three sprays were delivered horizontally.

14.1 Studies in Adults

Study 1

Study 1 was a Phase 3, multicenter, randomized, double-blind, placebo and active-controlled, parallel-groups study designed to compare the efficacy and safety of intranasally administered KOVANAZE to both tetracaine HCl alone and placebo, for providing dental anesthesia sufficient to allow completion of the standard dental procedure on a single maxillary tooth (#4-13) in adults.

A total of 110 patients were enrolled in two clinical centers and randomized to receive three 0.2 mL intranasal sprays of either KOVANAZE (n=44), tetracaine alone (n=44), or placebo (n=22). All randomized patients completed the study dental procedure.

Fifty-three percent (53%) of randomized patients were female and 76% were White, with a mean age of 35 years (range 18 to 73 years).

Eighty-four percent (95% CI: 70%, 93%) of KOVANAZE patients were able to complete the dental procedure without the need for rescue medication compared to 27% (95% CI: 15%, 43%) who received tetracaine alone and 27% (95% CI: 11%, 50%) who received placebo.

KOVANAZE had a lower success rate for dental procedures on the 2nd pre-molar (teeth #4 and #13) compared with more anterior teeth (#5 through #12): 63% for the 2nd pre-molars vs 96% for more anterior teeth.

In this trial, the median duration of a dental procedure successfully completed with KOVANAZE was 11 minutes, although one successfully completed dental procedure was as long as 43 minutes. Of the people that needed rescue medication in the KOVANAZE arm, they required it within the first 6 minutes following the start of the dental procedure.

Study 2

Study 2 was a Phase 3, multicenter, randomized, double-blind, parallel-groups study designed to compare the efficacy and safety of intranasally administered KOVANAZE to placebo, for providing dental anesthesia sufficient to allow completion of the standard dental procedure on a single maxillary tooth (#4-13) in adults.

A total of 150 adult patients were enrolled at three study centers and received either KOVANAZE (n=100) or placebo (n=50) as a dose of two or three 0.2 mL intranasal sprays. All except two randomized patients (one each in the KOVANAZE and placebo groups) completed the study dental procedure.

Fifty-five percent (55%) of randomized patients were female and 63% were White, with a mean age of 41 years (range 18 to 78 years).

Eighty-eight percent (95% CI: 80%, 94%) of KOVANAZE patients were able to complete the dental procedure without the need for rescue medication compared to 28% (95% CI: 16%, 43%) of patients who received placebo.

KOVANAZE had a lower success rate for dental procedures on the 2nd pre-molar (teeth #4 and #13) compared with more anterior teeth (#5 through #12): 64% for the 2nd pre-molars vs 96% for more anterior teeth.

14.2 Study in Children

Study 3

Study 3 was a Phase 3, multicenter, randomized, double-blind, parallel-groups study designed to compare the efficacy and safety of intranasally administered KOVANAZE to placebo for providing dental anesthesia sufficient to allow completion of the standard dental procedure on a single maxillary tooth (permanent teeth 4-13 or primary teeth A-J) for pediatric patients aged 3 through 17.

A total of 90 patients, 3 through 17 years of age inclusive, were enrolled at two study centers. Patients received one or two intranasal sprays of either KOVANAZE (n=60) or placebo (n=30) based on body weight: one 0.1 mL spray for patients weighing 10 kg to less than 20 kg; two 0.1 mL sprays for 20 kg to less than 40 kg; or two 0.2 mL sprays for patients weighing 40 kg to 60 kg; or three 0.2 mL sprays for patients weighing 60 kg or more.

In a 24-hour follow-up period, 84% of children in the KOVANAZE arm and 77% in the placebo arm were successfully treated with KOVANAZE with no differences in rescue medication requirements. Most children were discharged from the office within 48 hours.
or more. All except one randomized patient in the KOVANAZE group completed the study dental procedure.

Fifty-one percent (51%) of randomized patients were male and 89% were White, with a mean age of 8 years (range 3 to 17 years).

Even though a greater percentage of patients were able to complete the dental procedure without the need for rescue anesthesia for KOVANAZE: 77% for KOVANAZE (95% CI: 64%, 87%) compared to 53% for placebo (95% CI: 34%, 72%) an analysis by weight indicated that efficacy was only established for patients weighing 40 kg or more [see Table 3].

Table 3: Success Rates by Weight Group in the Pediatric Dental Patients (Study 3)

<table>
<thead>
<tr>
<th>Successful Anesthetic Response by Weight</th>
<th>KOVANAZE (N = 60)</th>
<th>Placebo (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 kg or more</td>
<td>18/20 (90%)</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td>20 to less than 40 kg</td>
<td>14/24 (58%)</td>
<td>5/12 (42%)</td>
</tr>
<tr>
<td>10 to less than 20 kg</td>
<td>14/16 (88%)</td>
<td>7/8 (88%)</td>
</tr>
</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING

KOVANAZE Nasal Spray is supplied as pre-filled, single-use sprayers containing a clear aqueous solution of 30 mg/mL of tetracaine hydrochloride (equivalent to 26.4 mg/mL tetracaine) and 0.5 mg/mL of oxymetazoline hydrochloride (equivalent to 0.44 mg/mL oxymetazoline). Each sprayer delivers 0.2 mL.

The product is available as:

NDC 69803-100-10: Box of 30 sprayers

Store between 2° and 8°C (36° and 46°F); excursions permitted between 0° and 15°C (32° and 59°F) [see USP controlled cold temperature].

Discard any unused solution. DO NOT use if drug is left out at room temperature for more than 5 days.

17 PATIENT COUNSELING INFORMATION

- Inform patients of the likelihood of expected side effects (including runny nose, nasal congestion, mild nose bleeds, dizziness, and/or a sensation of difficulty in swallowing) that should resolve within the same day. Instruct patients to contact their dentist or health care professional if these symptoms persist [see Adverse Reactions (6)].

- Advise patients to inform the dental practitioner if they are taking monoamine oxidase inhibitors (MAOIs), nonselective beta adrenergic antagonists, or tricyclic antidepressants [see Drug Interactions (7.1)].

- Instruct patients to avoid using oxymetazoline-containing products (such as Afrin® and other α-adrenergic agonists) within 24 hours prior to their scheduled dental procedure. [see Drug Interactions (7.2)].

- Advise patients of the signs and symptoms of hypersensitivity reactions and to seek immediate medical attention should they occur [see Warnings and Precautions (5.5)].

St. Renatus, LLC
Manufactured for:
St. Renatus, LLC
Fort Collins, CO 80526

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