IHEEZOTM (chloroprocaine hydrochloride ophthalmic gel) 3%, for topical ophthalmic use
Initial U.S. Approval: 1955

---INDICATIONS AND USAGE---
IHEEZOTM is an ester anesthetic indicated for ocular surface anesthesia. (1)

---DOSAGE AND ADMINISTRATION---
- The recommended dose of IHEEZOTM is 3 drops applied topically to the ocular surface in the area of the planned procedure. (2)
- IHEEZOTM may be reapplied as needed to maintain anesthetic effect. (2)

---DOSAGE FORMS AND STRENGTHS---
IHEEZOTM (chloroprocaine hydrochloride ophthalmic gel) 3% contains 24 mg of chloroprocaine hydrochloride per vial (800 mg). Clear, colorless to light yellow gel in single-patient-use vial. (3)

---CONTRAINDICATIONS---
IHEEZOTM is contraindicated in patients with a history of hypersensitivity to any component of this preparation. (4)

---WARNINGS AND PRECAUTIONS---
- Not for Injection or Intraocular Administration (5.1).
- Corneal Injury Due to Insensitivity (5.2).
- Corneal Opacification (5.3).
- For Administration by Healthcare Provider: IHEEZOTM is not intended for patient self-administration (5.5).

---ADVERSE REACTIONS---
Most common adverse reaction is mydriasis (approximately 25%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Harrow at 844.446.6979 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2022
FULL PRESCRIBING INFORMATION

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2 DOSAGE AND ADMINISTRATION
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3 DOSAGE FORMS AND STRENGTHS
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4 CONTRAINDICATIONS
IHEEZOTM is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

5 WARNINGS AND PRECAUTIONS
5.1 Not for Injection or Intraocular Administration
IHEEZOTM should not be injected or intraocularly administered.

5.2 Corneal Injury Due to Insensitivity
Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

5.3 Corneal Opacification
Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

5.4 Risk of Contamination
Do not touch the dropper tip to any surface as this may contaminate the gel.

5.5 For Administration by Healthcare Provider
IHEEZOTM is indicated for administration under the direct supervision of a healthcare provider. IHEEZOTM is not intended for patient self-administration.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect 201 patients undergoing various surgical ocular procedures in two placebo-controlled trials (Study 1 and Study 2). Patients in Study 1 were randomized to receive a single instillation of 3 drops of IHEEZOTM or placebo. Patients in Study 2 were
randomized to receive a single or multiple instillations of 1, 3 or 3+3 drops of IHEEZOTM or placebo.

The most common adverse reactions in these studies, (incidence greater than or equal to 5%) following IHEEZOTM administration were mydriasis, conjunctival hyperemia and eye irritation.

**Adverse Reactions Reported in Controlled Trials**

**Table 1. Adverse Reactions in 5% or more of IHEEZOTM Treated Patients in Studies 1 and 2**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>IHEEZOTM</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=151</td>
<td>N=50</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>39 (26%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>16 (11%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>9 (6%)</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

**Risk Summary**

There are no adequate and well-controlled studies of IHEEZOTM use in pregnant women to inform a drug associated risk. There are no animal reproduction studies for chloroprocaine.

**8.2 Lactation**

**Risk Summary**

There are no data on the presence of chloroprocaine in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for IHEEZOTM and any potential adverse effects on the breastfed infant from IHEEZOTM.

**8.4 Pediatric Use**

The safety and effectiveness of IHEEZOTM have not been established in pediatric patients.

**8.5 Geriatric Use**

No overall differences in safety or effectiveness of IHEEZOTM have been observed between elderly and younger patients.

**11 DESCRIPTION**

IHEEZOTM is a sterile, single-patient-use ophthalmic gel preparation for topical ocular anesthesia containing chloroprocaine hydrochloride as the active pharmaceutical ingredient. Chloroprocaine hydrochloride is an ester anesthetic. It is a water-soluble white crystalline powder and its chemical name is 2-(Diethylamino)ethyl 4-amino-2-chlorobenzoate monohydrochloride. The molecular weight is 307.22 and the molecular formula is C₁₃H₁₉ClN₂O₂·HCl. It is represented by the following structural formula:
IHEEZOTM contains:
Active: 30 mg of chloroprocaine hydrochloride (equivalent to 26 mg of chloroprocaine) per gram of gel.

Inactive ingredients: Hydroxyethyl Cellulose (HEC), and Water for Injection. The pH may be adjusted to 3.0 to 5.0 with Hydrochloric Acid. This product does not contain an antimicrobial preservative.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Chloroprocaine, like other local anesthetics, blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

12.3 Pharmacokinetics
The systemic exposure to chloroprocaine following topical ocular administration of IHEEZOTM has not been studied.

Elimination
Metabolism
Chloroprocaine is metabolized by plasma pseudocholinesterases and nonspecific esterases in ocular tissues. Chloroprocaine is rapidly metabolized in plasma by hydrolysis of the ester linkage by pseudocholinesterase. The hydrolysis of chloroprocaine results in the production of β-diethylaminoethanol and 2-chloro-4-aminobenzoic acid, which inhibits the action of the sulfonamides.

Excretion
Chloroprocaine plasma half-life in vitro is approximately 25 seconds in adults and approximately 43 seconds in neonates. The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH.
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Long-term studies in animals to evaluate carcinogenic potential of chloroprocaine have not been conducted.

Mutagenesis
2-chloroprocaine and the main metabolite, ACBA, were negative in the in vitro bacterial reverse mutation test (Ames assay) and the in vitro chromosome aberrations assay.

Impairment of Fertility
Studies in animals to evaluate the impairment of fertility have not been conducted with chloroprocaine.

14 CLINICAL STUDIES
14.1 Study 1 and 2
Study 1 (NCT04779606) and Study 2 (NCT04753710) were randomized, double-blinded placebo-controlled studies conducted to evaluate the efficacy, safety, and local tolerability of IHEEZOTM in 145 healthy volunteers.

In Study 1, 85 healthy male and female were randomized in a 4:1 ratio to receive a single ocular instillation of IHEEZOTM (N=68) or placebo (N=17). The double blinded treatment included a IHEEZOTM or a placebo dose of 3 drops instilled at 1 minute ± 15 seconds intervals in the right eye of each volunteer. The median age was 39 years (range 19 to 55 years); 59% female and 41% male.

In Study 2, 60 healthy male and female were randomized (40:20) to receive single or multiple ocular instillations of IHEEZOTM dose of 3 drops in the right eye. The median age was 25 years (range 18 to 59 years); 54% female and 46% male.

The efficacy in Study 1 and 2 was determined by proportion of patients achieving full conjunctival anesthesia evaluated by conjunctival pinching, 5 minutes after administration.

Efficacy results of Study 1
The proportion of subjects with successful anesthesia was 90% in IHEEZOTM group and 12% in the placebo group (p<0.01). The median time for the IHEEZOTM group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 14.3 minutes.

Efficacy results of Study 2
The proportion of subjects with successful anesthesia was 95% in the IHEEZOTM group and 20% in the placebo group (p<0.01). The median time for the IHEEZOTM group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 19.3 minutes.
14.2 Study 3
Study 3 (NCT04685538) was a randomized, prospective, multi-center, active-controlled, observer-masked study conducted to evaluate the efficacy and safety of IHEEZOTM (N=166) versus tetracaine ophthalmic solution 0.5% (N=172) in patients undergoing cataract surgery.

The primary endpoint was defined as the proportion of patients in each treatment group gaining successful anesthesia without any supplementation. On average, patients needed 1-1.5 minutes to obtain sufficient anesthesia to successfully perform the surgical procedure which lasted on average 22 minutes.

No patient treated with IHEEZOTM required supplemental treatment to complete the intended surgical procedure.

16 HOW SUPPLIED/STORAGE AND HANDLING
IHEEZOTM (chloroprocaine hydrochloride ophthalmic gel) 3% is supplied as a sterile, clear, colorless to light yellow gel in a single-patient-use vial. Each single-patient-use vial contains 24 mg chloroprocaine in 800 mg of gel.

Aluminum pouch containing 1 LDPE single-patient-use vial of IHEEZOTM. The outer surface of the vial is not sterile.

NDC 82667-300-01 Package of 1 unit of 1.25 mL single-patient-use vial (800 mg filled)
NDC 82667-300-10 Package of 10 units of 1.25 mL single-patient-use vials (800 mg filled)

Storage
Store at 15°C to 25°C (59°F to 77°F). Discard after use.

17 PATIENT COUNSELING INFORMATION

Eye Care Precaution
Do not touch the dropper tip to any surface as this may contaminate the gel.

Advise patients that their eyes will be insensitive for up to 20 minutes due to the effect of the anesthetic, and that care should be taken to avoid accidental injuries.

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