

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TYMBION ◊ safely and effectively. See full prescribing information for TYMBION.

TYMBION (lidocaine hydrochloride and epinephrine) otic solution

Initial U.S. Approval: 1948

INDICATIONS AND USAGE
TYMBION, a combination of an amide local anesthetic and an alpha- and beta-adrenergic agonist, is indicated for the induction of local anesthesia of the tympanic membrane, via iontophoresis using the Tula [®] Iontophoresis System, in pediatric (aged 6 months and older) and adult patients undergoing tympanostomy tube placement using the Tula Tube Delivery System. (1)
Limitations of Use
<ul style="list-style-type: none">TYMBION is for use ONLY with the Tula Iontophoresis System and cannot be used with any other iontophoresis device. TYMBION is not for use alone (i.e., without the Tula Iontophoresis System) and is not interchangeable with other lidocaine with epinephrine formulations.

DOSAGE AND ADMINISTRATION
<ul style="list-style-type: none">TYMBION is administered into the external ear canal through the Earset of the Tula Iontophoresis System. A low level of electrical current supplied by the Iontophoresis System results in penetration of lidocaine and epinephrine into the tympanic membrane. Once the iontophoresis process is complete, TYMBION is removed from the external ear canal by gravity or wicking. (2.2) TYMBION is to be used by healthcare professionals familiar with the administration of local anesthetics. (2.2)
DOSAGE FORM AND STRENGTH
<ul style="list-style-type: none">Otic Solution. Each mL of TYMBION contains 20 mg of lidocaine HCl and 10 mcg of epinephrine. (3)

CONTRAINDICATIONS
<ul style="list-style-type: none">Patients presenting with tympanic membrane perforation(s) or lacerations/ abrasions to the external auditory canal. (4) Patients with a history of sensitivity or allergic reaction to lidocaine HCl, tetracaine, epinephrine, or any hypersensitivity to local anesthetics of the amide type, or any component of the anesthetic drug formulation. (4) Patients with a familial history of insensitivity to lidocaine or other local anesthetics. (4)

WARNINGS AND PRECAUTIONS
<ul style="list-style-type: none">To minimize caloric stimulation that can cause patient dizziness, warm TYMBION before administering. (5.1) TYMBION, when used with the Tula Iontophoresis System, does not anesthetize the external auditory ear canal. (5.1) Refer to the Tula Iontophoresis System Instructions for Use for additional Warnings and Precautions related to the use of the device components of the Tula System.

ADVERSE REACTIONS
The most common adverse reactions (>2%) occurring in patients treated with TYMBION using the Tula Iontophoresis System were inadequate anesthesia and vertigo/dizziness. (6)
USE IN SPECIFIC POPULATIONS
The safety and effectiveness of TYMBION has been established in pediatric patients aged 6 months and older. The recommended dose for children is the same as adults, and is controlled by the electrical current delivery of the Tula Iontophoresis System. (8.4)
To report SUSPECTED ADVERSE REACTIONS, contact Smith & Nephew, Inc. at 1-800-343-5717 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch
See 17 for PATIENT COUNSELING INFORMATION
Revised: 11/2021

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FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

TYMBION, a combination of an amide local anesthetic and an alpha- and beta-adrenergic agonist, is indicated for the induction of local anesthesia of the tympanic membrane via iontophoresis using the Tula Iontophoresis System in pediatric (aged 6 months and older) and adult patients undergoing tympanostomy tube placement using the Tula Tube Delivery System.

Limitations of Use

- TYMBION is for use **ONLY** with the Tula Iontophoresis System and cannot be used with any other iontophoresis device.
- TYMBION is not for use alone (ie, without the Tula Iontophoresis System) and is not interchangeable with other lidocaine with epinephrine formulations.

DOSAGE AND ADMINISTRATION

2.1 Dosing

Each mL of TYMBION contains 20 mg lidocaine HCl, equivalent to 16.2 mg lidocaine, and 10 mcg of epinephrine. The typical volume of the external ear canal for children ages 6 months to 12 years is approximately 0.4 mL to 0.8 mL. The Tula Iontophoresis System tubing and reservoir accommodates approximately 0.6 mL.

2.2 General Instructions

Use TYMBION only in conjunction with the Tula Iontophoresis System. Full instructions for use of the Tula Iontophoresis System are provided with the Iontophoresis System. In brief, instill TYMBION into the external ear canal via Earsets connected to fitted Earplugs. The Tula Iontophoresis System applies an electrical current to the solution, which causes lidocaine and epinephrine to penetrate the tympanic membrane. After approximately 10 minutes, iontophoresis is complete and TYMBION is drained from the external ear canal by gravity or wicking. Iontophoresis can extend beyond 10 minutes if the program is paused or current is reduced per the Tula Iontophoresis System instructions for use. Assess adequate local anesthesia by lightly tapping the tympanic membrane with a dull otologic probe or the tip of the Tube Delivery System.

- Warm TYMBION to approximately body temperature prior to instilling in the external ear canal [see *Warnings and Precautions* (5.1)].
- Avoid touching the ear canal wall with otologic instruments [see *Warnings and Precautions* (5.1)]

2.3 Repeat Administration

The safety of repeat iontophoretic administration of TYMBION has not been evaluated in humans, and repeat administration (to the same ear) is not recommended. [see *Nonclinical Toxicology* (13.2)].

A nonclinical repeat dose study showed mild residual shifts in auditory brainstem response at 28 days after the final repeated dose, likely related to external ear canal debris or inflammation in the external ear canal or tympanic membrane. There was no adverse impact of the repeat TYMBION dosing on ossicular structures, ossicular mobility, cochlear hair cells, or on microscopic inner ear findings.

3 DOSAGE FORM AND STRENGTH

Otic Solution for iontophoretic delivery using only the Tula Iontophoresis System: TYMBION is a sterile, nonpyrogenic solution of lidocaine hydrochloride 2% (20 mg/mL, equivalent to lidocaine 16.2 mg/mL) and epinephrine 1:100,000 (0.01 mg/mL) in water; provided in 20 mL single-patient-use vials for iontophoretic administration using the Tula Iontophoresis System.

4 CONTRAINDICATIONS

- Iontophoretic administration of TYMBION is contraindicated in patients with tympanic membrane (TM) perforation(s), or lacerations or abrasions to the external auditory canal.
- Iontophoretic administration of TYMBION is contraindicated in patients with a history of sensitivity or allergic reaction to lidocaine HCl, tetracaine, epinephrine, or any hypersensitivity to local anesthetics of the amide type, or any component of the anesthetic drug formulation.
- Iontophoretic administration of TYMBION is contraindicated in patients with a familial history of insensitivity to lidocaine or other local anesthetics (e.g., history of inadequate anesthesia with dental local anesthetic agents).

5 WARNINGS AND PRECAUTIONS

5.1 Local (External Ear Canal and Tympanic Membrane) Effects

Although not noted during clinical trials, local edema and erythema was noted during preclinical animal studies upon iontophoretic administration of TYMBION. These effects were temporary in nature and generally resolved within 14 days of the procedure.

TYMBION should be warmed to approximately body temperature prior to instilling in the external ear canal. Cool drug placed into the ear canal may cause dizziness due to caloric stimulation.

TYMBION, when administered with the Tula Iontophoresis System, provides local anesthesia of the tympanic membrane, and not the external ear canal. Avoid impacting the ear canal wall with otologic instruments.

5.2 Middle Ear Effects

Iontophoretic administration of TYMBION is contraindicated in patients with perforation of the tympanic membrane. However, it is possible that a perforation is undetected by otoscopy and tympanometry, both of which are recommended prior to initiation of iontophoresis (see Tula Iontophoresis System Instructions For Use).

If TYMBION enters the middle ear, some may enter the vestibular system, leading to vestibular symptoms, such as vertigo and nausea. These symptoms may last from 4 to 8 hours, after which the drug dissipates, typically with no lingering effects.

5.3 Allergic Reactions

Allergic reactions have been reported for lidocaine in the literature. Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions. Allergic reactions may occur as a result of sensitivity either to local anesthetic agents, to bisulfites, or to the methylparaben used as a preservative. The detection of sensitivity by skin testing is of doubtful value.

TYMBION contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Patients allergic to para-amino-benzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

5.4 Systemic Reactions

Adverse experiences following the systemic administration of lidocaine are similar in nature to those observed with other amide local anesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage (particularly in the presence of a TM perforation), rapid absorption or inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

CNS manifestations are excitatory and/or depressant and may be characterized by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold, or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression, and arrest. The excitatory manifestations may be very brief or not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest. Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

Monitor neurological status, cardiovascular status, and vital signs during and after administration of TYMBION in patients suspected of experiencing systemic adverse reactions.

5.5 Methemoglobinemia

Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.

Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue TYMBION and any oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care; i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Local effects including edema and erythema [see *Warnings and Precautions* (5.1)]
- Middle ear effects including vertigo and nausea [see *Warnings and Precautions* (5.2)]
- Allergic reactions [see *Warnings and Precautions* (5.3)]
- Systemic reactions [see *Warnings and Precautions* (5.4)]

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 safety of TYMBION delivered via iontophoresis, using the Tula Iontophoresis System, was evaluated in four clinical trials; three in adult patients (n=90) and one in pediatric patients aged 6 months to 12 years (n=269). Study 1, a prospective, multicenter study in adult patients, and Study 2, a prospective, multicenter study in pediatric patients, evaluated the safety of iontophoretically administered TYMBION in patients undergoing tympanostomy tube placement. Safety was evaluated for up to three weeks in adult patients and up to 12 months in pediatric patients.

The most commonly reported drug-related adverse reactions (> 2% of patients) to occur in Study 1 or Study 2 with TYMBION are described in **Table 1**. One of the adverse reactions of vertigo and dizziness observed in Study 1 was considered to be a vestibular symptom resulting from TYMBION inadvertently entering the middle ear.

Adverse Reaction	Study 1 (%) (n/N)	Study 2 (%) (n/N)
Inadequate anesthesia*	3% (1/30)	4% (12/269)
Vertigo / Dizziness	7% (2/30)	-

*Inadequate anesthesia was defined as a response to the tympanic membrane tap assessment performed after TYMBION iontophoresis and prior to tympanostomy tube placement.

Adverse reactions related to the tympanostomy tubes, such as otorrhea and tube occlusion, are not included in the table, but can be found in the Tula System Instructions For Use.

6.2 Post-Marketing Experience

No post-marketing data exist for TYMBION.

7 DRUG INTERACTIONS

7.1 Monoamine Oxidase Inhibitors

The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe prolonged hypertension.

7.2 Drugs Associated with Methemoglobinemia

The toxic effects of local anesthetics are additive and their co-administration should be used with caution including monitoring for neurologic and cardiovascular effects related to local anesthetic systemic toxicity.

Patients who are administered local anesthetics may be at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics:

Examples of Drugs Associated with Methemoglobinemia

Class	Examples
Nitrates/Nitrites	nitric oxide, nitroglycerin, nitroprusside, nitrous oxide, articaene, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine
Antineoplastic agents	cyclophosphamide, flutamide, hydroxyurea, ifosfamide, rasburicase
Antibiotics	dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides
Antimalarials	chloroquine, primaquine
Anticonvulsants	phenobarbital, phenytoin, sodium valproate
Other drugs	acetaminophen, metoprolpramide, quinine, sulfasalazine

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on TYMBION use in pregnant women to inform risks associated with major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on the low systemic exposure associated with clinical administration of TYMBION, this product is expected to present minimal risk for maternal and fetal toxicity when administered to pregnant women.

In a published animal reproduction study, pregnant rats administered lidocaine by continuous subcutaneous infusion at doses approximately 49,000 times the estimated maximum delivered dose (MDD) of 0.098 mg/day during the period of organogenesis resulted in lower fetal body weights. In a published animal reproduction study, pregnant rats administered lidocaine containing 1:100,000 epinephrine, injected into the masseter muscle of the jaw or into the gum of the lower jaw at 590 times the estimated MDD on Gestation Day 11 resulted in developmental delays in neonates [see Data].

Data

Human Data

There are no data on TYMBION-related effects on pregnant women. Depending on the procedure performed, the type and amount of drug used, and the technique of drug administration, lidocaine can transfer across the placental barrier and act on the fetus.

Animal Data

In a published study, lidocaine administered to pregnant rats by continuous subcutaneous infusion during the period of organogenesis at 100, 250, and 500 mg/kg/day, did not produce any structural abnormalities, but did result in lower fetal weights at 500 mg/kg/day dose (approximately 49,000 times the estimated maximum delivered dose (MDD) on a mg/m² basis) in the absence of maternal toxicity.

In a published study, lidocaine containing 1:100,000 epinephrine at a dose of 6 mg/kg (approximately 590 times the MDD on a mg/m² basis) injected into the masseter muscle of the jaw or into the gum of the lower jaw of pregnant Long-Evans hooded rats on Gestation Day 11 resulted in developmental delays in the neonates. Developmental delays were observed for negative geotaxis, static righting reflex, visual discrimination response, sensitivity and response to thermal and electrical shock stimuli, and water maze acquisition. The developmental delays of the neonatal animals were transient, with responses becoming comparable to untreated animals later in life. The clinical relevance of the animal data is uncertain.

8.2 Lactation

Risk Summary

There are no data on the presence or absence of lidocaine or epinephrine in human milk after TYMBION administration with the Tula Iontophoresis System and there are no data on TYMBION-related effects on breastfed children or on the effect of milk production.

8.4 Pediatric Use

The safety and effectiveness of iontophoretically-administered TYMBION for local anesthesia of the tympanic membrane has been established in children 6 months of age and older, as supported by the clinical study conducted in pediatric patients [see *Adverse Reactions* 6.1, *Clinical Studies* 14].

The safety and effectiveness of TYMBION has not been established in pediatric patients younger than 6 months of age.

8.5 Geriatric Use

In a clinical trial in adult patients receiving tympanostomy tubes after iontophoresis with TYMBION [see *Clinical Studies* 14] there were 8 patients over the age of 64. No age-related differences in efficacy or safety were evident. However, clinical studies did not include sufficient numbers of patients age 65 and over to determine whether they respond differently than younger patients.

8.6 Hepatic Impairment

Patients with severe hepatic disease are at greater risk of developing toxic plasma concentrations because of their inability to normally metabolize lidocaine. However, the plasma exposure to iontophoretically-administered TYMBION is very small [see *Clinical Pharmacology* (12.2)].

8.7 Renal Impairment

Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

10 OVERDOSAGE

Clinical Presentation

Acute emergencies from local anesthetics are generally related to high plasma concentrations encountered during therapeutic use of local anesthetics or to unintended intravascular injection of local anesthetic solution.

Signs and symptoms of overdose include CNS symptoms (perioral paresthesia, dizziness, dysarthria, confusion, mental obtundation, sensory and visual disturbances, and eventually convulsions) and cardiovascular effects (that range from hypertension and tachycardia to myocardial depression, hypotension, bradycardia, and asystole).

Management of Local Anesthetic Overdose

The first consideration is prevention, best accomplished by careful and constant monitoring of the patient’s state of consciousness after local anesthetic administration. At the first sign of change, oxygen should be administered.

The first step in the management of convulsions, as well as undereventration or apnea due to unintended subarachnoid injection of drug solution, consists of immediate attention to the maintenance of a patent airway and assisted or controlled

ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to the use of local anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. Undereventration or apnea due to unintentional subarachnoid injection of local anesthetic solution may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

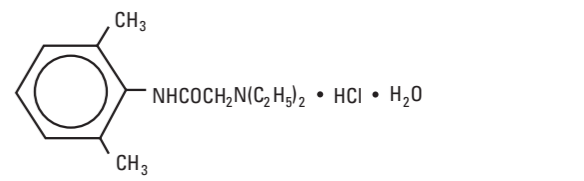
Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated, after initial administration of oxygen by mask, if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

Dialysis is of negligible value in the treatment of acute overdose with lidocaine HCl.

11 DESCRIPTION

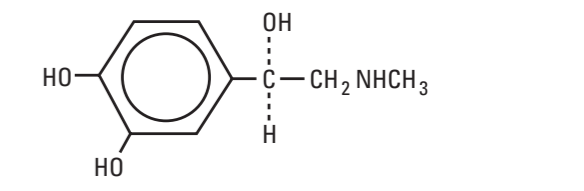
TYMBION otic solution is a sterile, nonpyrogenic solution of lidocaine hydrochloride (an amide local anesthetic) and epinephrine (an alpha and beta adrenergic agonist) in water; for iontophoretic administration with the Tula Iontophoresis System. TYMBION is provided in a 20 mL vial for single-patient use. TYMBION contains lidocaine HCl, 20 mg/mL equivalent to lidocaine 16.2 mg, epinephrine 10 mcg/mL, and sodium chloride 6 mg/mL. Sodium metabisulfite 0.5 mg/mL and citric acid, anhydrous 0.2 mg/mL are added as stabilizers. Methylparaben 1 mg/mL is added as a preservative, and the solution may contain hydrochloric acid to adjust pH to 4.5 (range 3.3 to 5.5).

Lidocaine Hydrochloride, USP is chemically designed 2-(diethylamino)-2’-6’-acetoxyllidide monohydrochloride monohydrate, a white powder freely soluble in water. It has the following chemical structure:



The chemical formula is C₁₄H₂₂N₂O-HCl·H₂O, and the molecular weight is 288.8.

Epinephrine, USP is a sympathomimetic (adrenergic) agent designated chemically as 4-[1-hydroxy-2 (methylamino) ethyl]-1,2 benzenediol, a white, microcrystalline powder. It has the following structural formula:



The chemical formula is C₉H₁₃NO₂·C₈H₉O₂, and the molecular weight is 333.3.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lidocaine is an amide local anesthetic. Lidocaine blocks sodium ion channels required for the initiation and conduction of neuronal impulses. Epinephrine is both an alpha- and beta-adrenergic receptor agonist. Epinephrine produces local vasoconstriction, which prolongs the effect of lidocaine by reducing local tissue clearance.

12.2 Pharmacodynamics

Hemodynamics

While the systemic exposure to iontophoretically-administered TYMBION is low, excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. With central neural blockade these changes may be attributable to block of autonomic fibers, a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system and/or the beta-adrenergic receptor stimulating action of epinephrine.

12.3 Pharmacokinetics

Absorption

The Tula Iontophoresis System provides an electrical dose of 6.36mAmin to drive ions of lidocaine and epinephrine into the tympanic membrane in a ~10-12 minute application, after which the drug is removed from the ear canal.

A randomized, double blind pharmacokinetics study was conducted to evaluate systemic exposure to lidocaine HCl and epinephrine from TYMBION administered using the Tula Iontophoresis System. Twenty-five healthy adult volunteers were randomized 3:2 to receive bilateral iontophoresis of TYMBION (n=15) or 2% lidocaine without epinephrine (n=10). Blood plasma samples were taken prior to the procedure, immediately after iontophoresis, and at 5, 15, 25, 35, 50, 80, 110, 170 and 230 minutes after iontophoresis. Maximum mean lidocaine concentration (C_{max}) was 2.25 ng/mL for TYMBION and 1.98 ng/mL for 2% lidocaine. Plasma levels (C_{max}) of epinephrine following bilateral iontophoretic administration of TYMBION (39.9 pg/mL) or 2% lidocaine (43.6 pg/mL) were within the normal range for endogenous epinephrine (30-50 pg/mL).

Factors such as acidosis and the use of central nervous system (CNS) stimulants and depressants affect the CNS levels of lidocaine HCl required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6 mcg free base per mL.

Distribution

Plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 µg of free base per mL, 60 to 80 percent of lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein. Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

Elimination

Metabolism

It is not known if lidocaine is metabolized in the tympanic membrane. If present systemically, lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of lidocaine or TYMBION have not been conducted.

A metabolite, 2,6-xylylidine, has been found to be carcinogenic in rats. The clinical significance is not known.

Mutagenesis

Genetic toxicology studies for lidocaine and epinephrine have not been conducted.

Impairment of Fertility

In a published study, female Sprague-Dawley rats were treated subcutaneously with lidocaine via osmotic pumps starting two weeks prior to mating, and reproductive effects were assessed. Rats dosed up to the high dose of 500 mg/kg/day (approximately 49,000 times the maximum delivered dose of 0.098 mg/day on a mg/m² basis) showed no effects on copulatory rate, pregnancy rate, numbers of corpora lutea, or implantations.

13.2 Animal Toxicity and/or Pharmacology

Local Irritation

In a repeat-dose ototoxicity study, guinea pigs were exposed to bilateral iontophoretic administration of TYMBION at various supra-clinical dosage levels and dosage frequencies including positive, negative, vehicle, and treatment controls. Iontophoretic dosing was supplied as 1x or 2x the human nominal dose of 6.36mAmin on two days (Day 1 and Day 5) or 1x for three days (Day 1, 5, and 10). Acute erythema and edema in the external ear canal occurred in all groups 48 hours after the final treatment, but was completely recovered by 28 days. Hearing loss as detected by auditory brainstem responses (ABR) occurred at 48 hours with recovery in most animals by 28 days. ABR abnormalities in 10% of ears in the treatment groups persisted to 28 days without recovery. The ABR abnormalities at 28 days were associated with treatment-related inflammation, otic debris, and tympanic membrane hyperplasia and fibrosis, which is consistent with conductive hearing loss. Ototoxicity, as defined by neurosensory damage to the cochlear hair cells in the organ of Corti, auditory nerve, or vestibular organ, did not occur under these test conditions. The relevance of these findings to humans is not clear. Clinical studies have not been conducted to test the safety of repeated dosing of TYMBION.

14 CLINICAL STUDIES

The safety and efficacy of iontophoretically-administered TYMBION used to facilitate tympanostomy tube placement was evaluated in two studies. In both studies, TYMBION was administered via the Tula Iontophoresis System in a physician’s office setting to provide local anesthesia of the tympanic membrane, followed by tympanostomy tube insertion using the Tula Tube Delivery System (TDS). Study 1 enrolled 30 adult patients (ages 21-83 years) and Study 2 enrolled 222 pediatric patients (ages 6 months through 12 years). An additional 47 pediatric patients were enrolled as “lead-in” cases in Study 2, data from which are included in the safety analyses only [see *Adverse Reactions* (6)].

Study 1 (NCT03197558):

Study 1 was a non-randomized, multicenter study in 30 adult patients (mean age 54.9 years, 43% male, 70% White/17% Black or African American/3% Asian/10% Other, 3% Hispanic or Latino) undergoing tympanostomy tube placement. TYMBION was administered either unilaterally or bilaterally using the Tula Iontophoresis System, as clinically indicated. Once iontophoresis was completed, local anesthesia of the tympanic membrane was assessed by lightly tapping the TM with a dull otologic instrument. Tympanostomy tubes were then placed using the Tula TDS and pain was assessed using a 0 to 100 mm Visual Analog Scale, where 0 = “no pain” and 100 = “worst possible pain”.

After TYMBION was administered with the Tula Iontophoresis System, 29/30 (97%) patients were determined by the investigator to have adequate local anesthesia to proceed with tympanostomy tube placement. In these 29 patients, tympanostomy tubes were successfully placed in 37 out of 37 targeted ears (100%). The mean (SD) VAS score upon tube insertion, using the higher of two scores if both ears were treated, was 9.4 mm (15.7 mm) (95% CI upper limit: 14.4) and the median was 3.0 mm (out of a maximum of 100 mm). The maximum VAS pain score reported was 64 mm.

Study 2 (NCT03323736):

Study 2 was a non-randomized multicenter study, with 17 sites in the U.S. and 1 site in Canada, in pediatric patients with recurrent acute otitis media or chronic otitis media with effusion requiring tympanostomy tube placement per clinical practice guidelines. To gain experience with the Tula technology, each investigator was required to treat two patients under general anesthesia in the operating room (OR lead-in cohort) using the TDS. A total of 68 procedures were performed in the OR lead-in cohort (mean age 3.4 years, 59% male, 78% White/9% Black or African American/4% Asian/9% other, 21% Hispanic or Latino). Each investigator was then required to treat two patients in the office lead-in cohort using the Tula Iontophoresis System. A total of 47 procedures were performed in the office lead-in cohort (mean age 4.8 years, 57% male, 77% White/13% Black or African American/2% Asian/8% other, 13% Hispanic or Latino). Once the OR and office lead-in patients were treated, the investigator could enroll patients in the pivotal treatment cohort. There were 120 patients aged 6 months through 4 years (mean age 2.3 years, 54% male, 91% White/8% Black or African American/3% Asian/2% Other, 9% Hispanic or Latino) and 102 patients aged 5 years through 12 years (mean age 7.6 years, 63% male, 76% White/18% Black or African American/ 0% Asian/7% Other, 20% Hispanic or Latino) treated with TYMBION using the Tula Iontophoresis System in the pivotal treatment cohort. All children were treated in a physician’s office setting, without the use of sedatives, anxiolytics, or papoose restraints. Once adequate local anesthesia was achieved, as assessed by lightly tapping the TM with a dull otologic instrument, tympanostomy tubes were placed using the Tula TDS. The study had one primary endpoint for children in the younger age group and two primary endpoints for children in the older age group.

Primary Endpoint 1: The percentage of children who had successful procedures (i.e., tubes placed in all indicated ears) had to be superior to a prespecified performance goal of 68%. Refer to **Table 2**.

Primary Endpoint 2: For children ages 5 to 12 years, the pain associated with tube placement had to be superior to (i.e., less than) the prespecified goal of 4.2 (out of a maximum score of 10) on the Faces Pain Scale – Revised (FPS-R). This endpoint was not evaluated in children under 5 years of age, based on their inability to reliably complete self-reported pain scales; however, pediatric distress in this age group was assessed using the Faces, Legs, Activity, Cry, Consolability (FLACC) Scale. Refer to **Table 4**.

Table 2 shows the results for the two primary endpoints. Procedural success was 86% in younger children and 89% in older children. The mean FPS-R score for tympanostomy tube placement was 3.3 (out of 10) with a median of 2.0. Mean and median FPS-R scores five minutes after tube insertion were 1.7 and 0, respectively.

Table 2: Primary Efficacy Endpoint Results (Study 2)

Primary Endpoints	Ages 6 months – 4 years	Ages 5 – 12 years
Procedural Success (rate) ^a	86% (103/120) (95% credible interval: 80%, 91%)	89% (91/102) (95% credible interval: 82%, 93%)
Tube Placement Tolerability (mean FPS-R score) ^b	N/A	3.3 (out of 10) (95% confidence interval: 2.6, 4.0)

^aThe Procedural Success endpoint was evaluated using a Bayesian Hierarchical framework. The success rate in each age group was compared to the performance goal of a 68% success rate. Success was declared for each age group if the lower bound of the 95% credible interval exceeded the performance goal of a 68% success rate. The study was designed to evaluate each age group separately, with data borrowing between groups.

^bThe mean Tube Placement Tolerability score was compared to a performance goal of 4.2. Success was declared if the upper bound of the 95% confidence interval was less than 4.2 on the FPS-R.

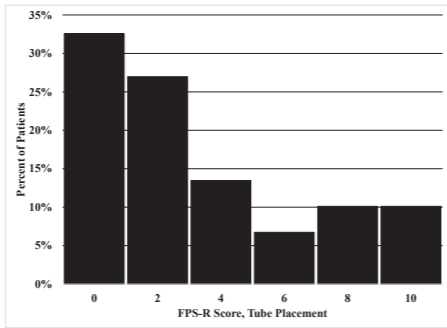
Table 3 summarizes the reasons for procedural failure in Study 2.

Table 3: Reasons for Procedure Failure (Study 2, Pivotal Cohort)

Reason for Procedure Failure	Pivotal Cohort, (%) (n/N)
Patient Behavior	5% (11/222)
Inadequate Anesthesia	3% (7/222)
Discomfort/Anxiety	2% (4/222)
Anatomic Challenges	1% (3/222)
Iontophoresis Intolerability	1% (2/222)
Partially Medialized Tube	0.5% (1/222)

For Primary Endpoint 2, the results for the full distribution of the FPS-R Tube Placement Tolerability scores upon tube placement are shown in **Figure 1**.

Figure 1: Distribution of Faces Pain Score – Revised (FPS-R) Tube Placement Scores for Patients Ages 5-12 Years Old (Study 2)



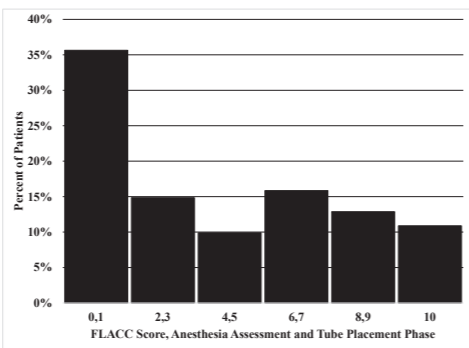
Pediatric distress was assessed in Study 2 using FLACC scores, reported on a scale of 0 (lowest) to 10 (highest). FLACC scores for each treated patient were assigned by a Core Lab, using video recordings of the procedures, scoring each major procedural phase separately. **Table 4** shows mean FLACC scores for key procedural phases for the younger and older pivotal treatment cohort patients who had successful procedures. **Figure 2** shows the full distribution of the FLACC scores during the procedural phase of the anesthesia assessment (tympanic membrane tap) and tympanostomy tube placement for the patients aged 6 months to 4 years old.

Table 4: Summary of FLACC Scores, by Procedure Phase and Age

FLACC Phase	Ages ^a 6 months – 4 years Mean (Standard Deviation)	Ages 5 years - 12 years Mean (Standard Deviation)
Pre-procedure Otoscopy	0.7 (2.0)	0.1 (0.7)
Earsset / Drug Fill	1.4 (2.8)	0.1 (0.5)
Iontophoresis	0.8 (2.1)	0.0 (0.1)
Tympanic Membrane Tap and Tube placement	4.0 (3.6)	0.4 (1.2)
3 min Post Procedure	1.3 (2.1)	0.2 (0.9)

^aSample sizes for younger children were 100-101 and for older children 87-88. Video data was not available for all phases for a few children due to video technical issues or obstructed views.

Figure 2: Distribution of FLACC Tube Placement Score for Patients Ages 6 months – 4 years (Study 2)



16 HOW SUPPLIED/STORAGE AND HANDLING

TYMBION is supplied in a single-patient-use 20 mL vial. TYMBION is only to be used with the Tula Iontophoresis System.

Store TYMBION at 20–25°C (68–77°F); excursions permitted between 15–30°C (59– 86°F) [see USP *Controlled Room Temperature*]. Retain TYMBION in the carton until use to protect the drug from light. Do not freeze.

Discard unused portion at the conclusion of the procedure.

The NDC code for TYMBION is 73257-001-01.

17 PATIENT COUNSELING INFORMATION

17.1 Risks Relating to the Iontophoresis Process

Advise patients that sensations of pressure, tingling, itching, or burning may be felt in the ear or at the location of the return electrode (used to complete the electrical circuit) during the iontophoretic administration of TYMBION. The Tula Iontophoresis System has physician-controllable features that may alleviate such sensations.

Advise patients that there may be some temporary redness at the site of the return electrode.

Advise patients that there is a risk of dizziness due to caloric stimulation, and a risk that anesthesia may not be adequate to complete the tube placement procedure.

Advise patients there is a risk of transient tongue numbness.

17.2 Local Effects

Inform patients that, although the product is contraindicated for use in patients with a tympanic membrane perforation, it is possible that perforations can be undetectable by otoscopy and tympanometry assessments. In such cases, TYMBION may inadvertently enter the middle ear, causing vertigo/dizziness and nausea, which may last for several hours. [see *Warnings and Precautions* (5.2)].

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