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

The Tula lontophoresis System provides an electrical dose of 6.36mAmin to drive ions of lidocaine and e into the tympanic membrane in a  $\sim$ 10-12 minute application, after which the drug is

Absorption

A randomized, double blind pharmacokinetics study was conducted to evaluate systemic exposure to lidocaine HCl and epinephrine from TYMBION administered using the Tula Iontophoresis Systen wenty-five healthy adult volunteers were randomized 3:2 to receive bilateral iontophoresis of YMBION (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 ( $\zeta_{max}$ ) was 2.25 ng/mL for TYMBION and 1.98 ng/mL for 2% flodcaine. Plasma levels ( $\zeta_{max}$ ) of epinephine following lialateral iontophoretic daministration 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 HCI required to produce overt systemic effects. Objective advers manifestations become increasingly apparent with increasing venous plasma levels above 6 mcg

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.

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 H-deallylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields

Approximately 90% or indocaine administered is excreted in the form of randoct instances. In less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2,

actions of these metabolites are similar to, but less potent than, those of lidocaine

6-dimethylaniline. The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2.0 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may Specific Populations

The effects of renal impairment, hepatic impairment, age, or sex on TYMBION pharmacokinetics have NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis

ong-term studies in animals to evaluate the carcinogenic potential of lidocaine or TYMBION have A metabolite, 2.6-xylidine, has been found to be carcinogenic in rats. The clinical significance is

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 matting, 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, pumpses of corpora lutase, or implicatations.

13.2 Animal Toxicity and/or Pharmacology Local Irritation

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 3) 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 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, oit debris, and tympanic membrane hyperplasia and fibrosis, which is consistent with conductive hearing loss. Ottoxicity, 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.

The safety and efficacy of iontophoretically-administered TYMBION used to facilitate tympanostom The safety and efficacy of ionfophoretically-administered IYMBION used to facilitate tympanoston tube placement was evaluated in two studies. In both studies, TYMBION was administered via the Tula lontophoresis System in a physician's office setting to provide local anesthesia of the tympani 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 I (NCI0319/558):
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 lontophoresis System, as clinically indicated. Once iontophoresis was completed, local anesthesia of the tympanic membrane was assessed by lightly tapping the TM with a dull totologic 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". Study 1 (NCT03197558):

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 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 (NCT03323736):

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 (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 2.6 years, 63% male, 14% Black or African American/3% Asian/2% Other, 9% Hispanic or Latino) and 102 patients aged 5 years through 12 years (mean age 2.6 years, 63% male, 14% Black or African American/3% Asian/2% Other, 20% Hispanic or Latino) treated with TYMBION using the Tula lontophoresis 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, 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

Table 2: Primary Efficacy Endpoint Results (Study 2)

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

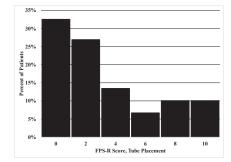
Primary Endpoints	Ages 6 months – 4 years	Ages 5 – 12 years
Procedural Success (rate) <sup>a</sup>	86% (103/120) (95% credible interval: 80%, 91%)	89% (91/102) (95% credible interval: 82%, 93%)
Tube Placement Tolerability (mean FPS-R score) b	N/A	3.3 (out of 10) (95% confidence interval: 2.6, 4.0)
<sup>a</sup> The Procedural Success endpoint was evalua group was compared to the performance goal bound of the 95% credible interval exceeded evaluate each age group separately, with dat	l of a 68% success rate. Success was d the performance goal of a 68% succes	leclared for each age group if the low
bThe mean Tube Placement Tolerability score		of 4.2. Success was declared if the

Table 3: Reasons for Procedure Failure (Study 2, Pivotal Cohort) Pivotal Cohort, (%) (n/N)

Anatomic Challenges 0.5% (1/222) For Primary Endpoint 2, the results for the full distribution of the FPS-R Tube Placement Tolerability

Figure 1: Distribution of Faces Pain Score – Revised (FPS-R) Tube Placement Scores for

scores upon tube placement are shown in Figure 1.



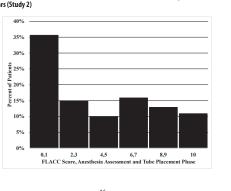
Pediatric distress was assessed in Study 2 using FLACC scores, reported on a scale of 0 (lowest) to 10 (highest). FLACC scores for each treated patient were assigned by a Core Lab, using video recordings of the procedures, scoring each major procedural phase separately. **Table 4** shows mean FLACC scores for key procedural phases for the younger and older pivotal treatment cohort patients who had

uccessful 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 <sup>a</sup> 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)
Earset / Drug Fill	1.4 (2.8)	0.1 (0.5)
lontophoresis	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)
	ere 100-101 and for older children 87-88.	,

Figure 2: Distribution of FLACC Tube Placement Score for Patients Ages 6 months



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 Store TYMBION at 20–25°C (68–77°F); excursions permitted between 15–30°C (59–86°F) [see USP ntrolled Room Temperature]. Retain TYMBION in the carton until use to protect the drug fron

light. Do not freeze. Discard unused portion at the conclusion of the procedure The NDC code for TYMBION is 73257-001-01.

PATIENT COUNSELING INFORMATION

17.1 Risks Relating to the lontophoresis Process Advise patients that sensations of pressure, tingling, itching, or burning may be felt in the ear or at administration of TYMBION. The Tula lontophoresis System has physician-controllable features that may alleviate such sensations.

Advise nationts that there is a risk of dizziness due to caloric stimulation, and a risk that anesthesia nay 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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TYMBION™

For lontophoresis with the Tula Iontophoresis System ONLY.

Single Patient Use Protect from light **Q**Tula

Initial U.S. Approval: 1948

HIGHLIGHTS OF PRESCRIBING INFORMATION

tube placement using the Tula Tube Delivery System. (1)

with other lidocaine with epinephrine formulations.

TYMBION (lidocaine hydrochloride and epinephrine) otic solution

TYMBION is to be used by healthcare professionals familiar with the administration of local anesthetics. (2.2)

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

———— INDICATIONS AND USAGE ———

YMBION, a combination of an amide local anesthetic and an alpha- and beta-adrenergic agonist, is

TYMBION is for use ONLY with the Tula lontophoresis System and cannot be used with any other

TYMBION is administered into the external ear canal through the Earset of the Tula lontophoresis

DOSAGE AND ADMINISTRATION —

indicated for the induction of local anesthesia of the tympanic membrane, via iontophoresis using the Tula® lontophoresis System, in pediatric (aged 6 months and older) and adult patients undergoing tympanostomy

TYMBION is not for use alone (i.e., without the Tula lontophoresis System) and is not interchangeable

DOSAGE FORM AND STRENGTH — Otic Solution. Each mL of TYMBION contains 20 mg of lidocaine HCl and 10 mcg of epinephrine. (3) 

Patients presenting with tympanic membrane perforation(s) or lacerations / abrasions to the external Patients with a history of sensitivity or allergic reaction to lidocaine HCI, 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 — To minimize caloric stimulation that can cause patient dizziness, warm TYMBION before administering.

TYMBION, when used with the Tula Iontophoresis System, does not anesthetize the external auditory

Refer to the Tula lontophoresis System Instructions for Use for additional Warnings and Precautions related to the use of the device components of the Tula System.

8.4. Pediatric Use

11. DESCRIPTION

8.6. Hepatic Impairment

8.7. Renal Impairment

13. NONCLINICAL TOXICOLOGY

14. CLINICAL STUDIES

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2. Animal Toxicity and/or Pharmacology

16. HOW SUPPLIED/STORAGE AND HANDLIN

17. PATIENT COUNSELING INFORMATION

Sections or subsections omitted from the full

prescribing information are not listed.

The most common adverse reactions (>2%) occurring in patients treated with TYMBION using the Tula lontophoresis 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 Tusker Medical Inc at 1-650-223-6900 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch See 17 for PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION: CONTENTS\*

DOSAGE AND ADMINISTRATION

INDICATIONS AND USAGE

DOSAGE FORM AND STRENGTH WARNINGS AND PRECAUTIONS

5.2. Middle Ear Effects 5.3. Allergic Reactions 5.4. Systemic Reactions

ADVERSE REACTIONS 5.1. Clinical Trials Experience

USE IN SPECIFIC POPULATIONS

DRUG INTERACTIONS . Monoamine Oxidase Inhibito

Revised: 11/2019

DOSAGE AND ADMINISTRATION 2.1 Dosing

2.2 General Instructions

Use TYMBION only in conjunction with the Tula lontophoresis System. Full instructions for use of the Tula lontophoresis System are provided with the lontophoresis System. In brief, instill TYMBION into the external ear canal via Earsets connected to fitted Earplugs. The Tula lontophoresis 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 lontophoresis System instructions for use. Assess adequate local anesthesia by lightly tapping the tympanic membrane 12. CLINICAL PHARMACOLOGY 12.1. Mechanism of Action 12.2. Pharmacodynamics

[see Warnings and Precautions (5.1)].

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 8 days after the final repeated dose, likely related to external ear canal debris or inflamn he external ear canal or tympanic membrane. There was no adverse impact of the repeat TYMBION osing on ossicular structures, ossicular mobility, cochlear hair cells, or on microscopic inner ear

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 ionto the Tula lontophoresis System in pediatric (aged 6 months and older) and adult patients undergoing tympanostomy tube placement using the Tula Tube Delivery System.

 TYMBION is for use ONLY with the Tula lontophoresis System and cannot be used with any other iontophoresis device.

TYMBION is not for use alone (ie, without the Tula lontophoresis System) and is not interchangeable with other lidocaine with epinephrine formulations.

Fach mL of TYMBION contains 20 mg lidocaine HCL equivalent to 16.2 mg lidocaine, and 10 mcg of nephrine. The typical volume of the external ear canal for children ages 6 months to 12 years is proximately 0.4 mL to 0.8 mL. The Tula lontophoresis System tubing and reservoir accommodate

· Warm TYMBION to approximately body temperature prior to instilling in the external ear canal

void touching the ear canal wall with otologic instruments [see Warnings and Precautions 2.3 Repeat Administration

CONTRAINDICATIONS (FM) perforation(s), or lacerations or abrasions to the external auditory canal.

anesthetics of the amide type, or any component of the anesthetic drug formulation. Interpreted or the aministration 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).

WARNINGS AND PRECAUTIONS

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 lontophoresis System, provides local anesthesia of the tympanic membrane, and not the external ear canal. Avoid impacting the ear canal wall with

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 lontophoresis System Instructions For Use). If TYMBION enters the middle ear, some may enter the vestibular system. leading to vestibular

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 bisuffites, or to the methylparaben used as a preservative. The detection of sensitivity by skin testing is of doubtful value.

Otic Solution for iontophoretic delivery using only the Tula lontophoresis System: TWISION 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 lontophoresis System.

Iontophoretic administration of TYMBION is contraindicated in patients with a history of sensitivity r allergic reaction to lidocaine HCl, tetracaine, epinephrine, or any hypersensitivity to local

5.1 Local (External Ear Canal and Tympanic Membrane) Effects

5.2 Middle Ear Effects

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 susceptibl 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

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 Jasma levels caused by excessive dosage (particularly in the presence of a TIM 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 ousness, respiratory depression, and arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging int ousness and respiratory arrest. Drowsiness following the administration of lidocaine is usuall an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption ardiovascular manifestations are usually depressant and are characterized by bradycardia, ypotension, and cardiovascular collapse, which may lead to cardiac arrest.

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

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 dehydroger 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, roma, arrhythmias, and death. Discontinue TYMBION and any oxidizing agents. Depending on the severity of the sines and symptoms, and interest may recond to support the care in a covened the same threat whether the same threat whe 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.

The following adverse reactions are discussed in more detail in other sections of the labeling: The lowering averse reactions are usuassed in more securing in other securities to the about the control 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)] 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 lontophoresis 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 a

dizziness observed in Study 1 was considered to be a vestibular symptom resulting from TYMBION inadvertently entering the middle ear. Table 1: Drug-Related Adverse Reactions with > 2% Incidence, by Patient

Study 1 
 Inadequate anesthesia\*
 3% (1/30)
 4% (12/269)

 Vertigo / Dizziness
 7% (2/30)

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.

Adverse Reaction

DRUG INTERACTIONS 7.1 Monoamine Oxidase Inhibitors The administration of local anesthetic solutions containing epinephrine or norepinephrine to patient receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe prolonged hypertension.

The toxic effects of local anesthetics are additive and their co-administration should be used with n including monitoring for neurologic and cardiovascular effects related to local anestheti

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

mples of Drugs Associated with Methemoglobinemia		
lass	Examples	
itrates/Nitrites ocal Anesthetics	nitric oxide, nitroglycerin, nitroprusside, nitrous oxide, articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine	
ntineoplastic agents	cyclophosphamide, flutamide, hydroxyurea, ifosfamide, rasburicase	
ntibiotics	dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides	
ntimalarials	chloroquine, primaquine	
nticonvulsants	phenobarbital, phenytoin, sodium valproate	

Other drugs acetaminophen, metoclopramide, quinine, sulfasalazine 8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy

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 dos (MDD) of 0.098 mg/day during the period of organogenesis resulted in lower fetal body weights. It 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

There are no data on TYMBION-related effects on pregnant women. Depending on the proce 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.

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 bhormalities, but did result in lower fetal weights at 500 mg/kg/day dose (approx 49,000 times the estimated maximum delivered dose (MDD) on a mg/m<sup>2</sup> 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-trans hooded rats on Gestation Day 11
resulted in developmental delays in the neonates. Developmental delays were observed for negal
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 neonata
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 afte

YMBION administration with the Tula Iontophoresis System and there are no data on TYMBIONrelated effects on breastfed children or on the effect of milk production. 3.4 Pediatric Use 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

8.5 Geriatric Use In a clinical trial in adult patients receiving tympanostomy tubes after iontophoresis with TYMBION in a clinical thair mout partiest section gy rypanisosing with the second partiest section of the second partiest section grant gran 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.

Acute emergencies from local anesthetics are generally related to high plasma concentration 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).

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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 underventilation 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, eeping in mind that drugs used to treat convulsions sometimes depress the circulation when

istered intravenously. Should convulsions persist despite adequate respiratory support, and 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 dru 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).

Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated, fter initial administration of oxygen by mask, if difficulty is encountered in the maintenance of patent airway or if prolonged ventilatory support (assisted or controlled) is indicated. Dialysis is of negligible value in the treatment of acute overdosage 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 lontophoresis 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 designated 2-(diethylamino)-2'.6'-acetoxylidide

NHCOCH<sub>2</sub>N(
$$C_2H_5$$
)<sub>2</sub> • HCI • H<sub>2</sub>  
CH<sub>3</sub>

The chemical formula is  $C_{14}H_{22}N_20$ +HCI+  $H_20$ ; and the molecular weight is 288.8. Epinephrine, USP is a sympathomimetic (adrenergic) agent designated chemically as 4-[1-hydroxy-2 nethylamino) ethyl]-1,2 benzenediol, a white, microcrystalline powder. It has the following

The chemical formula is  $C_9H_{13}NO_3 \cdot C_4H_6O_{6r}$  and the molecular weight is 333.3.

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 12.2 Pharmacodynamics Hemodynamics

While the systemic exposure to iontophoretically-administered TYMBION is low, excessive blood