HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Pliaglis® (Lidocaine and Tetracaine) Cream 7%/7% safely and effectively. See full prescribing information for Pliaglis® (Lidocaine and Tetracaine) Cream 7%/7%.

Pliaglis® (Lidocaine and Tetracaine) Cream 7%/7%, for topical use

Initial U.S. Approval: 2006

----------INDICATIONS AND USAGE----------

Pliaglis® Cream 7%/7% is a combination of lidocaine, an amide local anesthetic, and tetracaine, an ester local anesthetic, indicated for use on intact skin in adults to provide topical local analgesia for superficial dermatological procedures such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal. (1)

----------DOSAGE AND ADMINISTRATION----------

- Apply Pliaglis® Cream to intact skin 20 to 30 minutes prior to the procedure for dermal filler injection, ablative laser facial resurfacing, or pulsed-dye laser therapy. (2.1)
- For superficial dermatological procedures such as laser-assisted tattoo removal, apply Pliaglis® Cream 7%/7% to intact skin for 60 minutes prior to the procedure. (2.1)
- Amount of cream to apply is determined by size of treatment area. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Cream: 70 mg of lidocaine and 70 mg of tetracaine per gram (7%; 7%). (3)

----------CONTRAINDICATIONS----------

- Known history of sensitivity to lidocaine or tetracaine, or local anesthetics of the amide or ester type. (4)
- Para-aminobenzoic acid (PABA) hypersensitivity. (4)

----------WARNINGS AND PRECAUTIONS----------

- Use with caution in patients who may be more sensitive to systemic effects of lidocaine and tetracaine, including acutely ill or debilitated. (5.1)
- When used concomitantly with other products containing local anesthetic agents, amount absorbed from all formulations should be considered since systemic toxic effects are thought to be additive and potentially synergistic with lidocaine and tetracaine. (5.1)
- Do not apply to mucous membranes or broken or inflamed skin. Use only on intact skin. (5.1)
- Do not apply for longer times than those recommended or over larger surface areas than those recommended, which could result in absorption of lidocaine and tetracaine at doses that could lead to serious adverse effects. (5.1)
- Keep Pliaglis® Cream 7%/7% away from children and pets due to the risk of accidental exposure and resulting toxicity (5.2)
- Tetracaine has been associated with methemoglobinemia. Risk of methemoglobinemia is greatest for patients with congenital or idiopathic methemoglobinemia, and infants under age of twelve months who are receiving treatment with methemoglobin-inducing agents. (5.3)
- Allergic reactions have been associated with lidocaine, tetracaine, and other components of Pliaglis® Cream 7%/7%. (5.4)
- Avoid contact with eyes due to possibility of severe eye irritation. (5.5)
- Patients with severe hepatic disease or pseudocholinesterase deficiency, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations of lidocaine and tetracaine. (5.7)

----------ADVERSE REACTIONS----------

Most common local reactions were erythema (47%), skin discoloration (16%), and edema (14%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Taro Pharmaceuticals U.S.A., Inc. at 1-866-923-4914 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Use with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the systemic toxic effects are thought to be additive and potentially synergistic with lidocaine and tetracaine. (7.1)
- When used concomitantly with other products containing local anesthetic agents, amount absorbed from all formulations should be considered since systemic toxic effects are thought to be additive and potentially synergistic with lidocaine and tetracaine. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Lidocaine is excreted into human milk and it is not known if tetracaine is excreted into human milk. (8.3)
- Safety and effectiveness of Pliaglis® Cream 7%/7% in pediatric patients have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Issued: 10/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Pliaglis® Cream 7%/7% is a combination of lidocaine, an amide local anesthetic, and tetracaine, an ester local anesthetic, and is indicated for use on intact skin in adults to provide topical local analgesia for superficial dermatological procedures such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Pliaglis® Cream 7%/7% should only be applied to intact skin.

For use in adults only.

- For superficial dermatological procedures such as dermal filler injection, non-ablative laser facial resurfacing, or pulsed-dye laser therapy, apply Pliaglis® Cream 7%/7% to intact skin for 20 to 30 minutes prior to the procedure. See Table 1 for instructions on the amount to apply.
- For superficial dermatological procedures such as laser-assisted tattoo removal, apply Pliaglis® Cream 7%/7% to intact skin for 60 minutes prior to the procedure. See Table 1 for instructions on the amount to apply.

The dose of Pliaglis® Cream 7%/7% that provides effective local dermal analgesia depends on the duration of the application. Although not specifically studied, a shorter duration of application may result in a less complete dermal analgesia or a shorter duration of adequate dermal analgesia.

2.2 Dosage Information

Determine the amount of drug to apply.

The amount (length) of Pliaglis® Cream 7%/7% that should be dispensed is determined by the size of the area to be treated (see Table 1).

(a) Using the ruler supplied on the carton, squeeze out and measure the amount of Pliaglis® Cream 7%/7% that approximates the amount required to achieve proper coverage.

(b) Spread Pliaglis® Cream 7%/7% evenly and thinly (approximately 1 mm or the thickness of a dime) across the treatment area using a flat-surfaced tool such as a metal spatula or tongue depressor.

(c) After waiting the required application time, remove the Pliaglis® Cream 7%/7% by grasping a free-edge with your fingers and pulling it away from the skin.

Table 1. Amount of Pliaglis® Cream 7%/7% According to Treatment Site Surface Area

Surface Area of Treatment Site (cm^2)	Length of Lidocaine and Tetracaine Cream for 1 mm Thickness (cm)	Weight of Pliaglis® Cream 7%/7% Dispensed (g)
10	3	1
20	6	3
40	12	5
80	24	11
100	30	13
150	46	20
200	61	26
250	76	33
300	91	40
350	106	46
400	121	53

2.3 Important Dosage and Administration Instructions

Important Dosage and Administration instructions include:

- Remove Pliaglis® Cream 7%/7% if skin irritation or a burning sensation occurs during application.
- In order to minimize the risk of systemic toxicity, do not exceed the recommended amount of drug to apply or the duration of the application [*see Overdosage (10)*].
- Avoid eye contact with Pliaglis® Cream 7%/7%.
- Wash hands after handling Pliaglis® Cream 7%/7%.
- Upon removal from the treatment site, discard the used Pliaglis® Cream 7%/7% in a location that is out of the reach of children and pets. Access to Pliaglis® Cream 7%/7% by children or pets should be prevented during usage and storage of the product [*see WARNINGS and PRECAUTIONS (5.2)*].

3 DOSAGE FORMS AND STRENGTHS

Each gram of lPliaglis® Cream 7%/7% contains lidocaine 70 mg and tetracaine 70 mg and is a smooth, white to off-white, viscous cream.

4 CONTRAINDICATIONS

- Pliaglis® Cream 7%/7% is contraindicated in patients with a known history of sensitivity to lidocaine or tetracaine, local anesthetics of the amide or ester type, or to any other component of the product [*see Warnings and Precautions (5.4)*].
- Pliaglis® Cream 7%/7% is contraindicated in patients with para-aminobenzoic acid (PABA) hypersensitivity.

5 WARNINGS AND PRECAUTIONS

5.1 Overexposure

- Application of Pliaglis® Cream 7%/7% for longer times than those recommended or application of Pliaglis® Cream 7%/7% over larger surface areas than those recommended could result in absorption of lidocaine and tetracaine at doses that could lead to serious adverse effects [*see Overdosage (10)*].
- When Pliaglis® Cream 7%/7% is used concomitantly with other products containing local anesthetic agents, consider the amount absorbed from all formulations since the systemic toxic effects are thought to be additive and potentially synergistic with lidocaine and tetracaine.
- Pliaglis® Cream 7%/7% is not recommended for use on mucous membranes or on areas with a compromised skin barrier because these uses have not been adequately studied. Application to broken or inflamed skin may result in toxic blood concentrations of lidocaine and tetracaine from increased absorption.
- Use Pliaglis® Cream 7%/7% with caution in patients who may be more sensitive to the systemic effects of lidocaine and tetracaine, including the acutely ill or debilitated.

5.2 Risks of Secondary Exposure to Children and Pets

Used Pliaglis® Cream 7%/7% contains a large amount of lidocaine and tetracaine. The potential exists for a small child or pet to suffer serious adverse effects from ingesting Pliaglis® Cream 7%/7%, although this risk with lPliaglis® Cream 7%/7% has not been evaluated. After use, replace the cap securely on the tube. It is important to store and dispose of Pliaglis® Cream 7%/7% out of the reach of children and pets.

5.3 Methemoglobinemia

- Several local anesthetics, including tetracaine, have been associated with methemoglobinemia. The risk of methemoglobinemia is greatest for patients with congenital or idiopathic methemoglobinemia, and infants under the age of twelve months who are receiving treatment with methemoglobin-inducing agents.
- Very young patients or patients with glucose-6-phosphate dehydrogenase deficiencies are more susceptible to methemoglobinemia.
- Patients taking concomitant drugs associated with drug-induced methemoglobinemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, and quinine are also at greater risk for developing methemoglobinemia.
- There were no reports of methemoglobinemia in the trials of Pliaglis® Cream 7%/7%; however, providers are cautioned to carefully apply Pliaglis® Cream 7%/7% to ensure that the doses, areas of application, and duration of application are consistent with those recommended for the intended population.

5.4 Allergic Reactions

Allergic or anaphylactoid reactions associated with lidocaine, tetracaine, or other components of Pliaglis® Cream 7%/7% can occur. They are characterized by urticaria, angioedema, bronchospasm, and shock. If an allergic reaction occurs, it should be managed by conventional means. Lidocaine and tetracaine is contraindicated in patients with known hypersensitivity reactions to lidocaine, tetracaine, or local anesthetics of the amide or ester type.

5.5 Eye Irritation

Avoid contact of Pliaglis® Cream 7%/7% with the eyes based on the findings of severe eye irritation with the use of similar products in animals. Also, the loss of protective reflexes may predispose to corneal irritation and potential abrasion. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

5.6 Vaccinations

Lidocaine has been shown to inhibit viral and bacterial growth. The effect ofPliaglis® Cream 7%/7% on intradermal injections of live vaccines has not been determined.

5.7 Special patient populations

- Use Pliaglis® Cream 7%/7% with caution in patients who may be more sensitive to the systemic effects of lidocaine and tetracaine particularly the acutely ill or debilitated.
- Patients with severe hepatic disease or pseudocholinesterase deficiency, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations of lidocaine and tetracaine.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

However, the adverse reaction information from clinical trials does provide a basis for identifying the adverse events that appear to be related to drug use and for approximating their incidence in clinical practice.

Pliaglis® Cream 7%/7% has been evaluated for safety in 2159 persons undergoing a superficial dermal procedure. Pliaglis® Cream 7%/7% was studied in 11 placebo-controlled and 1 active-controlled trials, and in open-label safety trials. All 2159 persons were exposed to only a single application of Pliaglis® Cream 7%/7%. Adverse reactions were assessed by collecting spontaneously reported adverse events, and observations made on formal evaluation of the skin for specific reactions.

Most common adverse events in clinical trials

Localized Reactions: During or immediately after treatment with Pliaglis® Cream 7%/7%, the skin at the site of treatment may develop erythema, blanching or edema. In clinical studies, the most common local reactions were erythema (47%), skin discoloration (e.g., blanching, ecchymosis, and purpura) (16%), and edema (14%). There were no serious adverse events. However, one patient withdrew due to burning pain at the treatment site.

Other Localized Reactions: The following dermal adverse events occurred in 1% or less of Pliaglis® Cream 7%/7% -treated patients: ecchymosis, petechial rash, vesiculobullous rash, perifollicular erythema, perifollicular edema, pruritus, rash, maculopapular rash, dry skin, contact dermatitis, and acne.

Systemic (Dose-Related) Reactions: Across all trials, 19 subjects experienced a systemic adverse event, 15 of whom were treated with Pliaglis® Cream 7%/7% and 4 with placebo. The frequency of systemic adverse events was greater for the Pliaglis® Cream 7%/7% group (1%) than the placebo group (0.3%). The most common systemic adverse events were headache, vomiting, dizziness, and fever, all of which occurred with a frequency of <1%. Other systemic reactions were syncope, nausea, confusion, dehydration, hyperventilation, hypotension, nervousness, paresthesia, pharyngitis, stupor, pallor, and sweating.

Systemic adverse effects of lidocaine and tetracaine are similar in nature to those observed with other amide and ester local anesthetic agents, including CNS excitation and/or depression (lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensation of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Signs of CNS toxicity may start at plasma concentrations of lidocaine at 1000 ng/mL. The plasma concentrations at which tetracaine toxicity may occur are less well characterized; however, systemic toxicity with tetracaine is thought to occur with much lower plasma concentrations compared with lidocaine. The toxicity of co-administered local anesthetics is thought to be at least additive. Cardiovascular manifestations may include bradycardia, hypotension and cardiovascular collapse leading to arrest.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Pliaglis® Cream 7%/7%.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Eye disorders: Eyelid swelling
- Skin: Pruritus, Rash, Skin Burning Sensation, Erythema, Urticaria
- Other: Drug ineffective

7 DRUG INTERACTIONS

7.1 Antiarrhythmic Drugs

Pliaglis® Cream 7%/7% should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the systemic toxic effects are thought to be additive and potentially synergistic with lidocaine and tetracaine.

7.2 Local Anesthetics

When Pliaglis® Cream 7%/7% is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations should be considered since the systemic toxic effects are thought to be additive and potentially synergistic with lidocaine and tetracaine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. No adequate and well-controlled studies have been conducted in pregnant women. Pliaglis® Cream 7%/7% should be used during pregnancy only if the potential benefit justifies risk to the fetus. Lidocaine was not teratogenic in rats at doses up to 60 mg/kg (8-fold higher than the level of lidocaine contained in the lowest approved dose of Pliaglis® Cream 7%/7% based on a mg/m^2 body surface area comparison). Lidocaine was not teratogenic in rabbits at doses up to 15 mg/kg (4-fold higher than the level of lidocaine in the lowest approved dose of Pliaglis® Cream 7%/7% on a mg/m^2 basis).

Tetracaine was not teratogenic in rats given subcutaneous doses up to 10 mg/kg or in rabbits up to 5 mg/kg (equivalent to the level of tetracaine in the lowest approved dose of Pliaglis® Cream 7%/7% on a mg/m^2 basis). Lidocaine and tetracaine given as a 1:1 eutectic mixture of 10 mg/kg each was not teratogenic in rats (equivalent to the level of the active components in the lowest approved dose of Pliaglis® Cream 7%/7% on a mg/m^2 basis. Lidocaine and tetracaine given as a 1:1 eutectic mixture of 5 mg/kg each was not teratogenic in rabbits (equivalent to the level of the active components in the lowest approved dose of Pliaglis® Cream 7%/7% on a mg/m^2 basis).

Lidocaine containing 1:100,000 epinephrine at a dose of 6 mg/kg (approximately equivalent to the level of lidocaine in the lowest approved dose Pliaglis® Cream 7%/7% on a mg/m^2 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, lead to developmental delays in neonatal behavior among offspring. 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. Pre- and post-natal maturational, behavioral, or reproductive development was not affected by maternal subcutaneous administration of tetracaine during gestation and lactation up to doses of 7.5 mg/kg (equivalent to the level of tetracaine in the lowest approved dose of Pliaglis® Cream 7%/7% on a mg/m^2 basis).

8.2 Labor and Delivery

Neither lidocaine nor tetracaine is contraindicated in labor and delivery. In humans, the use of lidocaine for labor neuraxial analgesia has not been associated with an increased incidence of adverse fetal effects either during delivery or during the neonatal period. Tetracaine has also been used as a neuraxial anesthetic for cesarean section without apparent adverse effects on offspring. Should Pliaglis® Cream 7%/7% be used concomitantly with other products containing lidocaine and/or tetracaine, total doses contributed by all formulations must be considered.

8.3 Nursing Mothers

Lidocaine is excreted into human milk and it is not known if tetracaine is excreted into human milk. Therefore, caution should be exercised when Pliaglis® Cream 7%/7% is administered to a nursing mother since the milk:plasma ratio of lidocaine is 0.4 and is not determined for tetracaine. In a prior report, when lidocaine was used as an epidural anesthetic for cesarean section in 27 women, a milk:plasma ratio of 1.07 ±0.82 was found by using AUC values. Following single dose administration of 20 mg of lidocaine for a dental procedure, the point value milk:plasma ratio was similarly reported as 1.1 at five to six hours after injection. Thus, the estimated maximum total daily dose of lidocaine delivered to the infant via breast milk would be approximately 36 mcg/kg. Based on these data and the low concentrations of lidocaine and tetracaine found in the plasma after topical administration of Pliaglis® Cream 7%/7% in recommended doses, the small amount of these primary compounds and their metabolites that would be ingested orally by a suckling infant is unlikely to cause adverse effects [*see CLINICAL PHARMACOLOGY (12.3)*].

8.4 Pediatric Use

Safety and effectiveness of Pliaglis® Cream 7%/7% in pediatric patients have not been established.

Unintended exposure in pediatric patients could possibly lead to serious adverse effects [*see WARNINGS and PRECAUTIONS (5.2)*]. In a trial of Pliaglis® Cream 7%/7% in pediatric patients aged 5 to 17 years undergoing venipuncture (blood draw or intravenous line placement), Pliaglis® Cream 7%/7% applied for 30 minutes failed to show efficacy over placebo in reducing the pain associated with the procedure.

8.5 Geriatric Use

Of the total number of subjects treated with Pliaglis® Cream 7%/7% in controlled clinical studies, 161 subjects were 65 years and older, while 50 subjects were over 75 years of age. No overall differences in safety and effectiveness were observed between these subjects and younger subjects.

However, increased sensitivity in individual patients aged 65 years and older cannot be ruled out [*see CLINICAL PHARMACOLOGY (12.3)*].

10 OVERDOSAGE

Application of 59 g of Pliaglis® Cream 7%/7% over 400 cm^2 for up to 120 minutes to adults produces peak plasma concentrations of lidocaine of 220 ng/mL. Toxic levels of lidocaine (>5000 ng/mL) cause CNS toxicity, including the risk of seizure. Signs of CNS toxicity may start at plasma concentrations of lidocaine as low as 1000 ng/mL, and the risk of seizures generally increases with increasing plasma levels. Very high levels of lidocaine can cause respiratory arrest, coma, decreases in cardiac output, total peripheral resistance and mean arterial pressure, ventricular arrhythmias and cardiac arrest.

Tetracaine is associated with a profile of systemic CNS and cardiovascular adverse events similar to lidocaine, although toxicity associated with tetracaine is thought to occur at lower doses compared to lidocaine. The toxicity of co-administered local anesthetics is thought to be at least additive. In the absence of massive topical overdose or oral ingestion, other etiologies for the clinical effects or overdosage from other sources of lidocaine, tetracaine or other local anesthetics should be considered.

The management of overdosage includes close monitoring, supportive care and symptomatic treatment. Dialysis is of negligible value in the treatment of acute overdosage of lidocaine or tetracaine.

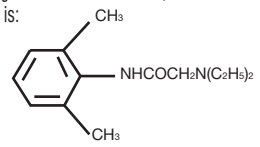
11 DESCRIPTION

Pliaglis® Cream 7%/7% is a topical local anesthetic cream that formsa pliable peel on the skin when exposed to air. The drug formulation is an emulsion in which the oil phase is a 1:1 eutectic mixture of lidocaine 7% and tetracaine 7%. The eutectic mixture has a melting point below room temperature and therefore both local anesthetics exist as a liquid oil rather than as crystals.

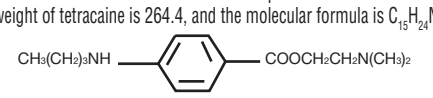
The net weight of lidocaine is 2.1 g and of tetracaine is 2.1 g per 30 g tube.
The net weight of lidocaine is 4.2 g and of tetracaine is 4.2 g per 60 g tube.
The net weight of lidocaine is 7.0 g and of tetracaine is 7.0 g per 100 g tube.

Lidocaine, an amide local anesthetic, is chemically designated as acetamide,2-(diethylamino)-N-(2,6-dimethylphenyl) and has an octanol:water partition ratio of 182 at pH 7.3.

The molecular weight of lidocaine is 234.3, and the molecular formula is $C_{14}H_{22}N_2O$. The structural formula is:



Tetracaine, an ester local anesthetic, is chemically designated as 2-dimethylaminoethyl 4-n-butyl-aminobenzoate and has an octanol:water partition ratio of 5370 at pH 7.3. The molecular weight of tetracaine is 264.4, and the molecular formula is $C_{15}H_{24}N_2O_2$. The structural formula is:



Each gram of Pliaglis® Cream 7%/7% contains lidocaine 70 mg and tetracaine 70 mg in a 1:1 eutectic mixture and it also contains the following inactive ingredients: dibasic calcium phosphate, methylparaben, petrolatum, polyvinyl alcohol, propylparaben, purified water, and sorbitan monopalmitate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lidocaine is an amide-type local anesthetic agent and tetracaine is an ester-type local anesthetic agent. Both lidocaine and tetracaine block sodium ion channels required for the initiation and conduction of neuronal impulses which, in certain instances, results in local anesthesia. When applied to intact skin, Pliaglis® Cream 7%/7% provides local dermal analgesia by the release of lidocaine and tetracaine from the peel into the skin.

12.2 Pharmacodynamics

Duration of analgesia was evaluated using a pinprick test in 40 adult volunteers. The median duration of analgesia was 11 hours. There was no difference between the 30-minute and 60-minute Pliaglis® Cream 7%/7% application periods with respect to the mean for time to return of sensation. However, 55% of Pliaglis® Cream 7%/7% treated subjects still reported diminished sensation at the end of the 13-hour study period.

12.3 Pharmacokinetics

Absorption: The amount of lidocaine and tetracaine systemically absorbed from Pliaglis® Cream 7%/7% is directly related to both the duration of application and the surface area over which it is applied, Table 2.

Application of 59 g of Pliaglis® Cream 7%/7% over 400 cm^2 for up to 120 minutes to adults produces peak plasma concentrations of lidocaine of 220 ng/mL. Tetracaine plasma levels were not measurable (<0.9 ng/mL). Systemic exposure to lidocaine, as measured by C_{max} and $AUC_{0\text{-}24}$, was proportional to the application area, and increased with application time up to 60 minutes.

Table 2. Absorption of lidocaine and tetracaine following application of Pliaglis® Cream 7%/7%

Lidocaine and tetracaine cream (g)	Area (cm^2)	Age Range (yr)	n	Application Time (min)	Drug Content (g)	Mean C_{max} (ng/mL)	Mean T_{max} (hr)
21	400	18-64	4	30	Lidocaine, 1.5	49	4.0
					Tetracaine, 1.5	<0.9	na
33	400	18-64	4	60	Lidocaine, 2.3	96	2.8
					Tetracaine, 2.3	<0.9	na
31	400	≤ 65	6	60	Lidocaine, 2.2	48	3.8
					Tetracaine, 2.2	<0.9	na

na=not applicable

Distribution: When lidocaine is administered intravenously to healthy volunteers, the steady-state volume of distribution is approximately 0.8 to 1.3 L/kg. At lidocaine concentrations observed following the recommended product application, approximately 75% of lidocaine is bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 mg/mL of free base) the plasma protein binding of lidocaine is concentration dependent. Lidocaine crosses the placental and blood brain barriers, presumably by passive diffusion. CNS toxicity may typically be observed around 5000 ng/mL of lidocaine; however, a small number of patients reportedly may show signs of toxicity at approximately 1000 ng/mL [*see OVERDOSAGE (10)*]. Volume of distribution and protein binding have not been determined for tetracaine due to rapid hydrolysis in plasma.

Metabolism: It is not known if lidocaine or tetracaine is metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites, including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. The major metabolic pathway of lidocaine, sequential N-deethylation to MEGX and GX, is primarily mediated by CYP1A2 with a minor role of CYP3A4. The metabolite, 2,6- xylidine, has unknown pharmacologic activity. Following intravenous administration of lidocaine, MEGX and GX concentrations in serum range from 11% to 36% and from 5% to 11% of lidocaine concentrations, respectively. Serum concentrations of MEGX were about one-third the serum lidocaine concentrations.

Tetracaine undergoes rapid hydrolysis by plasma esterases. Primary metabolites of tetracaine include para-aminobenzoic acid and diethylaminoethanol, both of which have an unspecified activity.

Elimination: The half-life of lidocaine elimination from the plasma following intravenous administration is approximately 1.8 hr. Lidocaine and its metabolites are excreted by the kidneys. More than 98% of an absorbed dose of lidocaine can be recovered in the urine as metabolites or parent drug. Less than 10% of lidocaine is excreted unchanged in adults, and approximately 20% is excreted unchanged in neonates. The systemic clearance is approximately 8 to 10 mL/min/kg. During intravenous studies, the elimination half-life of lidocaine was statistically significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours). The half-life and clearance for tetracaine has not been established for humans, but hydrolysis in the plasma is rapid.

Special Populations

Elderly: After application of 31g of Pliaglis® Cream 7%/7% over 400 cm^2 for 60 minutes, mean peak plasma levels of lidocaine were 48 ng/mL for elderly patients (>65 years of age, mean 68.0 ± 3.2 years, n = 6). These levels are similar to or lower than those for younger patients receiving similar amounts of Pliaglis® Cream 7%/7%.

Cardiac, Renal and Hepatic Impairment: No specific pharmacokinetic studies were conducted. The half-life of lidocaine may be increased in patients with cardiac or hepatic dysfunction. There is no established half-life for tetracaine due to rapid hydrolysis in the plasma.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either lidocaine or tetracaine.

Mutagenesis: The mutagenic potential of lidocaine base and tetracaine base has been determined in the *in vitro* Ames bacterial reverse mutation assay, the *in vitro* chromosome aberration assay using Chinese hamster ovary cells, and the *in vivo* mouse micronucleus assay. Lidocaine was negative in all three assays. Tetracaine was negative in the *in vitro* Ames assay and the *in vivo* mouse micronucleus assay. In the *in vitro* chromosome aberration assay, tetracaine was negative in the absence of metabolic activation, and equivocal in the presence of metabolic activation.

Impairment of Fertility: Lidocaine did not affect fertility in female rats when given via continuous subcutaneous infusion via osmotic minipumps up to doses of 250 mg/kg/day (35-fold higher than the level of lidocaine contained in the lowest approved dose of Pliaglis® Cream 7%/7% based on a mg/m^2 body surface area comparison). Lidocaine treatment did not affect overall fertility in male rats when given as subcutaneous doses up to 60 mg/kg (8-fold higher than the level of lidocaine contained in the lowest approved dose of Pliaglis® Cream 7%/7% based on a mg/m^2 basis), although the treatment caused an increased copulatory interval and led to a dose-related decrease in homogenization resistant sperm head count, daily sperm production, and spermatogenic efficiency. Tetracaine did not affect fertility in male or female rats when given as subcutaneous doses up to 7.5 mg/kg (equivalent to the level of tetracaine in the lowest approved dose of Pliaglis® Cream 7%/7% on a mg/m^2 basis).

14 CLINICAL STUDIES

In four clinical trials, adult patients were treated with Pliaglis® Cream 7%/7% or placebo prior to undergoing a superficial dermatologic procedure. Drug was applied for 20 or 30 minutes for dermatologic procedures such as dermal filler injection, pulsed dye laser therapy, and facial laser resurfacing. Drug was applied for 60 minutes for laser-assisted tattoo removal. Treatment with Pliaglis® Cream 7%/7% resulted in statistically significantly less pain compared to placebo treatment, as measured by a 100 mm visual analog scale (VAS). Patient efficacy ratings are shown in Table 3.

Table 3. Summary of patient evaluations following application of Pliaglis® Cream 7%/7% and placebo

	Mean VAS score	
Dermatologic Procedure	**Pliaglis® Cream 7%/7%**	**Placebo**
20 Min Application		
Pulsed Dye Laser Therapy (N=80)	16	31
30 Min Application		
Non-Ablative Laser Facial Resurfacing (N=54)	21	38
Dermal Filler Injections (N=70)	24	37
60 Min Application		
Laser-Assisted Tattoo Removal (N=62)	39	59

16 HOW SUPPLIED/STORAGE AND HANDLING

Pliaglis® Cream (70 mg of lidocaine and 70 mg of tetracaine in 1 gram), 7% / 7%, appears smooth and white to off-white and is available as the following: NDC 71800-631-15 30 gram tube

Refrigerate at 2 to 8°C (36 to 46°F). Do not freeze.

Pliaglis® Cream 7%/7% can be stored at room temperature for up to 3 months. Discard Pliaglis® Cream 7%/7% after storing at room temperature for 3 months.

17 PATIENT COUNSELING INFORMATION

Prior to treatment, advise patient of the following:

- Pliaglis® Cream 7%/7% is intended for use in a clinical setting under the supervision of a healthcare provider, and is not for home use by patients.
- Pliaglis® Cream 7%/7% is contraindicated in patients with a known history of sensitivity to lidocaine, tetracaine, local anesthetics of the amide or ester type, or any other component of the product and in patients with para-aminobenzoic acid (PABA) hypersensitivity.
- Pliaglis® Cream 7%/7% should be used with caution in patients who may be more sensitive to the systemic effects of lidocaine and tetracaine, including the acutely ill, the debilitated, and those with compromised hepatic function. Patients with severe hepatic disease or pseudocholinesterase deficiency are at greater risk of developing toxic plasma concentrations.
- Pliaglis® Cream 7%/7% should be used with caution in patients receiving class I antiarrhythmics and/or other local anesthetics, because the systemic toxic effects may be additive and potentially synergistic with lidocaine and tetracaine.
- Pliaglis® Cream 7%/7% should not be used if the patient has a history of methemoglobinemia.
- Contact of Pliaglis® Cream 7%/7% with the eyes should be avoided. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.
- Pliaglis® Cream 7%/7% is not for use on mucous membranes or on broken skin.
- If skin irritation or a burning sensation occurs during application, the product should be removed.
- If signs of an allergic or anaphylactoid reaction (urticaria, angioedema, bronchospasm, and shock) occur, instruct patients to seek immediate emergency help.
- Topical application of local anesthetics such as Pliaglis® Cream 7%/7% may lead to diminished or blocked sensation in the treated skin; therefore, patients should avoid inadvertent trauma (rubbing, scratching, or exposure to heat or cold) before complete sensation returns.
- The effect of Pliaglis® Cream 7%/7% on intradermal injections of live vaccines has not been determined.

Manufactured by:
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