PRODUCT MONOGRAPH

PrPLIAGLIS™

Lidocaine and Tetracaine Cream

Lidocaine 7% and Tetracaine 7%

Topical Anesthetic for Dermal Analgesia

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PLIAGLIS™

Lidocaine and Tetracaine Cream

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Topical	Cream / Lidocaine 7% + Tetracaine 7%	Calcium hydrogen phosphate (anhydrous), methylparaben, paraffin (white, soft), polyvinyl alcohol, propylparaben, purified water, sorbitan monopalmitate.

INDICATIONS AND CLINICAL USE

PLIAGLIS (lidocaine 7% and tetracaine 7%) cream is indicated in adults to produce local dermal analgesia on intact skin:

- prior to dermatological procedures: pulsed dye laser therapy, laser assisted hair removal, non ablative laser facial resurfacing, collagen and other dermal filler injections, vascular access, laser assisted tattoo removal, and laser leg vein ablation.

PLIAGLIS should only be used for the approved indications because safety and efficacy have not been determined for other uses. PLIAGLIS cream should be applied to skin areas 400cm^2 or less and for the time recommended only. (see WARNINGS AND PRECAUTIONS; ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION).

Geriatrics (> 65 years of age):
Evidence from clinical studies, where 110 patients over 65 years of age, of which 49 were over 75 years of age participated, suggests no overall differences in safety and effectiveness. However, increased sensitivity in patients 65 years and older cannot be ruled out. (See WARNINGS AND PRECAUTIONS, Special Populations)

Pediatrics (less than 18 years of age):
PLIAGLIS is not indicated for use in pediatric patients less than 18 years of age because safety and efficacy have not been established in this age group.

The safety and efficacy of PLIAGLIS have not been studied for pain associated with vaccines in infants (from birth to 15 months) or older children, nor has the efficacy of vaccines been evaluated in this context.

The safety and efficacy of PLIAGLIS have not been studied for pain associated with circumcision.

In a trial of PLIAGLIS in pediatric patients aged 5-17 years undergoing venipuncture (blood draw or intravenous line placement), PLIAGLIS applied for 30 minutes failed to show efficacy over placebo in reducing the pain associated with the procedure.

CONTRAINDICATIONS

PLIAGLIS (lidocaine 7% and tetracaine 7%) cream is contraindicated in:

- patients with a known history of sensitivity to lidocaine or tetracaine, or local anesthetics of the amide or ester type;
- patients with para-aminobenzoic acid (PABA) hypersensitivity;
- patients with a known history of sensitivity to any other component of the product. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- patients with congenital or idiopathic methemoglobinemia;
- Procedures requiring large amounts of PLIAGLIS over large areas of the body (more than 400 cm^2).

WARNINGS AND PRECAUTIONS

For external use only. Not for home use by patient. Only for use in clinical settings.

PLIAGLIS should not be applied to open wounds, irritated skin, mucous membranes including; mouth, lips, nose, eyes, ears, genital or anal areas.

General

Any remaining peel residue should be carefully wiped with a compress after removing PLIAGLIS (lidocaine 7% and tetracaine 7%) cream peel.

Even dried PLIAGLIS removed after use may contain a large amount of lidocaine and tetracaine. The potential exists for a small child or pet to suffer serious adverse effects from chewing or ingesting new or used PLIAGLIS. It is important to store and dispose of PLIAGLIS out of reach and sight of children and pets.

The treated area should not be occluded before removing PLIAGLIS from the skin. The use of an occlusive dressing may increase the absorption of lidocaine and tetracaine and could lead to serious adverse reactions.

PLIAGLIS is not to be used 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.

The safety of more than one application of PLIAGLIS has not been evaluated. Repeated doses of PLIAGLIS (lidocaine and tetracaine) may increase blood levels of lidocaine and tetracaine.

PLIAGLIS should be used with caution in patients who may be more sensitive to the systemic effects of lidocaine and tetracaine including acutely ill, debilitated, or elderly patients, and patients with severe hepatic impairment (see DOSAGE AND ADMINISTRATION).

PLIAGLIS should not be applied for a longer time or on larger areas than recommended as it could lead to absorption of doses of lidocaine and tetracaine associated with serious adverse reactions (see DOSAGE AND ADMINISTRATION).

Cardiovascular

PLIAGLIS should be used with caution in patients with cardiac impairment, and in subjects with increased sensitivity to systemic circulatory effects of lidocaine and tetracaine, such as the acutely ill or debilitated.

Hematologic

Several local anaesthetics, including tetracaine, have been associated with methemoglobinemia. The risk of methemoglobinemia is greatest for patients with congenital or idiopathic methemoglobinemia.

Patients taking 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. However caution should be exercised to ensure that the doses, areas of application, and duration of application are consistent with those recommended for the intended population.

Hepatic/Biliary/Pancreatic

PLIAGLIS should be used with caution in patients with hepatic or renal impairment. Because amide-type local anesthetics are metabolized by the liver, these drugs, especially repeated doses, should be used cautiously in patients with hepatic disease. For patients with severe hepatic disease, a reduced capacity to metabolize local anesthetics may increase the risk of developing toxic plasma concentrations.

Ophthalmologic

Contact with eyes should be avoided. PLIAGLIS should be used with caution in the proximity of the eyes as it causes corneal irritation if it comes into contact with the cornea. In addition, the loss of protective reflexes may allow corneal irritation and potential abrasion. If PLIAGLIS

comes into contact with the eye, the eye should be rinsed immediately with water or sodium chloride solution and should be protected until sensation returns.

Lidocaine and lidocaine-containing topical analgesics can have ototoxic effects if they come into contact with the tympanic membrane. Care should be taken when PLIAGLIS is applied near the ear.

Sensitivity/Resistance
Rare allergic or anaphylactoid reactions associated with lidocaine, tetracaine or other ingredients in PLIAGLIS can occur. Tetracaine may be associated with a higher incidence of such reactions than lidocaine.

Ester-type local anesthetic agents such as tetracaine are metabolized to PABA derivatives by plasma pseudocholinesterases and may therefore cause allergic reactions in people sensitive to PABA.

PLIAGLIS contains methyl and propyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).

Sexual Function/Reproduction
There are no fertility data for the use of lidocaine and tetracaine in humans.

Skin
PLIAGLIS should not be used on mucous membranes or on broken or irritated skin.

Patients must take extra care to avoid inadvertent trauma to the skin (through scratching, rubbing or exposure to extreme temperatures) whilst under the local anaesthetic effects of PLIAGLIS.

Systemic adverse reactions
Systemic adverse reactions following appropriate use of PLIAGLIS are unlikely (see CLINICAL PHARMACOLOGY, Pharmacokinetics). 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 (light-headedness, 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). 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 as low as 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.

Vaccination

PLIAGLIS is not indicated for use as an analgesic in vaccine injections. The efficacy of vaccines has not been evaluated in this context. Lidocaine has bactericidal and antiviral properties in concentrations above 0.5-2%. Therefore the effectiveness of vaccines could be compromised.

Patient Counselling Information

The Consumer Information leaflet should be provided when PLIAGLIS is dispensed/administered.

Patients receiving PLIAGLIS should be given the following instructions by the physician:

1. Patients should be advised that even dried PLIAGLIS removed after use may contain a large amount of lidocaine and tetracaine. The potential exists for a small child or pet to suffer serious adverse effects from chewing or ingesting new or used PLIAGLIS. It is important to store and dispose of PLIAGLIS out of reach and sight of children and pets.

2. Patients should be advised that they should not use PLIAGLIS if they are sensitive to lidocaine, tetracaine, or any amide or ester-type local anesthetics. Nor should they use PLIAGLIS if they are sensitive to PABA, the parabens methyl and propyl parahydroxybenzoate, or any component of the product.

3. Patients should be advised that they should not use PLIAGLIS if they have congenital or idiopathic methemoglobinemia.

4. Patients should be advised that PLIAGLIS should not be used on areas larger than 400 cm^2 , or for longer than the recommended time (up to 60 minutes).

5. Patients should be instructed that PLIAGLIS must not be used on mucosal membranes, open wounds, or irritated skin, and that it should not be covered and must be left to dry.

6. Patients should be advised not to use PLIAGLIS too close to the eyes or inside the ear.

7. Patients should be advised to take extra care to avoid inadvertent trauma to the skin (through scratching, rubbing or exposure to extreme temperatures) whilst under the local anaesthetic effects of PLIAGLIS.

8. Patients should be advised that PLIAGLIS should only be used for the indicated uses and that PLIAGLIS is not indicated for vaccination or for use in children less than 18 years of age.

Special Populations

PLIAGLIS is contraindicated for patients with congenital or idiopathic methemoglobinemia (see also CONTRAINDICATIONS). Patients with glucose-6-phosphate dehydrogenase deficiency are more susceptible to drug-induced methemoglobinemia.

Pregnant Women:

There are no data from the use of PLIAGLIS during pregnancy. Lidocaine crosses the placental barrier and may be absorbed by the fetal tissues. There are limited data from the use of both drugs during the first trimester of pregnancy.

Nursing Women:

Lidocaine is excreted into human milk and it is not known if tetracaine is excreted into human milk. No effects on the breastfed newborn/infant are anticipated since low concentration of lidocaine and tetracaine are found in the plasma after topical administration of PLIAGLIS at recommended doses. Care should be taken that PLIAGLIS is not applied to the breast of breastfeeding women.

Pediatrics:

PLIAGLIS is not indicated for use in pediatric patients less than 18 years of age because safety and efficacy have not been established in this age group.

The safety and efficacy of PLIAGLIS have not been studied for pain associated with vaccines in infants (from birth to 15 months) or older children, nor has the efficacy of vaccines been evaluated in this context.

The safety and efficacy of PLIAGLIS have not been studied for pain associated with circumcision.

In a trial of PLIAGLIS in pediatric patients aged 5-17 years undergoing venipuncture (blood draw or intravenous line placement), PLIAGLIS applied for 30 minutes failed to show efficacy over placebo in reducing the pain associated with the procedure.

Geriatrics (> 65 years of age):

Greater sensitivity of some older individuals cannot be ruled out. There are insufficient data to evaluate quantitative differences in systemic plasma levels of lidocaine and tetracaine between geriatric and non-geriatric patients following application of PLIAGLIS.

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).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The total number of patients experiencing adverse reactions in controlled clinical trials was 740 (50%) for the PLIAGLIS (lidocaine 7% and tetracaine 7%) cream treatment group (N = 1480) and 485 (40%) for the placebo group (N = 1229).

The most frequently reported adverse reactions in the PLIAGLIS treatment group in controlled studies were erythema (42%), skin discolouration (12%) and skin oedema (8%). Most adverse reactions were mild and transient in nature. However, one patient withdrew from a controlled study due to burning pain at the treatment site and a second subject withdrew from an open-label study due to severe skin oedema at the treatment site.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In controlled clinical trials, 1480 subjects received PLIAGLIS and 1229 subjects received placebo or vehicle. The adverse reactions reported in at least 1% of the patients treated with PLIAGLIS in the controlled clinical trials are listed in Table 1 below.

Table 1: Commonly Reported Adverse Events Reported in Controlled Clinical Trials

System Organ Class / Preferred Term	PLIAGLIS[a] n=1480 (%)	Placebo[b] n=1229 (%)
Skin and subcutaneous tissue disorders		
Erythema	(42)	(34)
Skin Discolouration	(12)	(8)
Skin Oedema	(8)	(4)

[a] Includes Developmental A PLIAGLIS Formulation, Developmental B PLIAGLIS Formulation, Developmental C PLIAGLIS Formulation, Final PLIAGLIS Formulation (including Final 4-88 and Final 5-88);
[b] Includes 100 subjects that received a Vehicle Control.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following less common adverse events have been experienced with PLIAGLIS in clinical trials.

Table 2: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials

System Organ Class / Preferred Term	PLIAGLIS[a] n=1480 (%)	Placebo[b] n=1229 (%)
Eye Disorders		
Eyelid edema	(<0.1%)	0
General Disorders and Administration Site Conditions		
Pain	(<1%)	(<1%)
Application site reaction	(<1%)	(<1%)
Nervous System Disorders		
Paresthesia	(<0.1%)	0
Skin and subcutaneous tissue disorders		
Pruritis	(<1%)	(<1%)
Pain of skin	(<1%)	0
Pallor	(<0.1%)	(<0.1%)
Skin burning sensation	(<0.1%)	(<0.1%)
Swelling face	(<0.1%)	(<0.1%)
Skin exfoliation	(<0.1%)	0
Skin irritation	(<0.1%)	0

[a] Includes Developmental A PLIAGLIS Formulation, Developmental B PLIAGLIS Formulation, Developmental C PLIAGLIS Formulation, Final PLIAGLIS Formulation (including Final 4-88 and Final 5-88);

[b] Includes 100 subjects that received a Vehicle Control.

Systemic Events

Across all trials, 19 subjects experienced a systemic adverse event, 15 of who were treated with PLIAGLIS and 4 with placebo. The frequency of systemic adverse events was greater for the PLIAGLIS 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 events were syncope, nausea, confusion, dehydration, hyperventilation, hypotension, nervousness, paresthesia, pharyngitis, stupor, pallor, and sweating.

Overall, systemic adverse reactions following appropriate use of PLIAGLIS are unlikely to occur, due to the small dose absorbed (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics)

Post-Market Adverse Drug Reactions

Table 3 is based on post-market spontaneous adverse event reports. The percentages shown are calculated by dividing the number of adverse events reported to the company by the estimated number of patients exposed to the drug during the same time period. The causal relationship between PLIAGLIS and the emergence of these events has not been established.

Table 3: PLIAGLIS Post-Market Spontaneous Adverse Event Reports

System Organ Class / Preferred Term	Frequency			
	≥1%	<1% and ≥0.1%	<0.1% and ≥0.01%	<0.01%
Eye disorders				
Corneal epithelium defect				X
Eye pain				X
Eye swelling				X
Keratitis				X
Vision blurred				X
Immune system disorders				
Anaphylactic shock				X
Infections and infestations				
Keratitis herpetic				X
Injury, poisoning and procedural complications				
Eye burns				X
Investigations				
Blood pressure increased				X

DRUG INTERACTIONS

Overview

No drug-drug interaction studies have been conducted on PLIAGLIS (lidocaine 7% and tetracaine 7%) cream.

Since PLIAGLIS is for short duration topical administration, it is less likely that metabolic drug-drug interactions of clinical significance can occur due to the resultant low systemic exposure to lidocaine and tetracaine.

Ester derivatives such as tetracaine that are hydrolysed to para-aminobenzoic acid may antagonise the activity of aminosalicylic acid or sulfonamides.

Lidocaine has been found to potentiate the neuromuscular blocking effects of suxamethonium (succinylcholine) in both human and animal studies.

Drug-Drug Interactions

Antiarrhythmic Drugs: There is an increased risk of myocardial depression when amide-type local anaesthetics such as lidocaine are given with antiarrhythmics. PLIAGLIS 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. Caution is advised when using Class III antiarrhythmic drugs concomitantly with PLIAGLIS due to potential pharmacodynamic or pharmacokinetic

interactions, or both. Patients treated with Class III antiarrhythmic drugs (e.g. amiodarone) should be kept under close surveillance and ECG monitoring should be considered, since cardiac effects of these drugs and PLIAGLIS may be additive.

Local Anesthetics: When PLIAGLIS is used concomitantly with other products containing local anaesthetic agents or agents structurally related to amide-type local anesthetics, 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.

CYP3A4 inhibitors: Lidocaine is eliminated primarily by hepatic metabolism, primarily by CYP1A2 with a minor role of CYP3A4 responsible for the formation of metabolites. Numerous drugs including HIV protease inhibitors, macrolides, azole antifungals, amiodarone and cimetidine are CYP3A4 inhibitors and may change lidocaine metabolism and lead to elevated serum levels.

Lidocaine and cocaine, when taken together are additive depressants of GABA-mediated responses *in vitro* and likely synergistic convulsants.

Esterases: Tetracaine is metabolized by esterases and caution should be exercised in using cholinesterase inhibitors such as antimyasthenics, cyclophosphamide, echothiophate, isoflurophate, and thiopeta. These agents may lead to increased risk of toxicity.

Methemoglobinemia: In patients treated concomitantly with PLIAGLIS and other methemoglobin-inducing agents including but not limited to sulfonamides, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine and quinine, PLIAGLIS may induce the formation of methemoglobin and result in overt clinical signs of methemoglobinemia.

Drug-Food Interactions

PLIAGLIS is for topical use only. Drug-food interactions have not been studied.

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

PLIAGLIS (lidocaine 7% and tetracaine 7%) cream should only be applied to intact skin.

> Do not reapply to treated area after the procedure. If your procedure has to be repeated, the treated area must have time to fully recover before using PLIAGLIS again.

PLIAGLIS should be used in the treatment location where the procedure will be performed.

Conditions where dosing may require adjustment:

- in acutely ill, debilitated or elderly patients, and patients with severe hepatic impairment who are more sensitive to systemic effects due to increased blood levels of lidocaine and tetracaine
- in patients who are administered other local anesthetics or amide type local anesthetics (see DRUG INTERACTIONS)
- in debilitated patients, or those with impaired elimination, smaller application areas are recommended to avoid toxicity.

PLIAGLIS should only be used for the approved indications because safety and efficacy have not been determined for other uses. PLIAGLIS cream should be applied to skin areas 400cm^2 or less and for the time recommended only.

For use in adults only.

- For superficial dermatological procedures such as needle insertions (e.g. dermal filler injection) or facial laser ablation, apply PLIAGLIS to intact skin for 20-30 minutes prior to the procedure. See Table 2 for instructions on the amount to apply.
- For superficial dermatological procedures such as laser-assisted tattoo removal, apply PLIAGLIS to intact skin for 60 minutes prior to the procedure. See Tables 4 and 5 for instructions on the amount to apply.

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)

Recommended Dose and Dosage Adjustment

For less painful dermatological procedures PLIAGLIS should be applied to intact skin at a thickness of approximately 1 millimetre (mm) for 20-30 minutes (approximately 1.3 g of cream per 10 cm^2). After the required time, the peel must then be removed from the skin prior to the procedure.

For more painful dermatological procedures PLIAGLIS should be applied onto intact skin at a thickness of approximately 1 millimetre (mm) for 60 minutes (approximately 1.3 g of cream per 10 cm^2). After the required time, the peel must then be removed from the skin prior to the procedure.

The amount (length) of PLIAGLIS that should be dispensed is determined by the size of the area to be treated (see Table 4).

Table 4: Dosage and Administration Information

Surface Area of Treatment site(cm^2)	Length of PLIAGLIS for 1 mm Thickness (cm)	Weight of PLIAGLIS Dispensed (g)
10	3	1.3
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	52

Table 5: Visual Comparator Reference Chart

cm^2	**Area Reference**
10	Approximately the size of a two dollar coin ("toonie").
40	Approximately the size of a credit card.
80	Approximately the size of two credit cards.
200	Approximately the size of a standard postcard.
400	Approximately the size of 2 standard postcards.

The maximum application area should not exceed 400 cm^2.

Administration

Squeeze out and measure the amount of PLIAGLIS that approximates the amount required to achieve proper coverage. Then spread PLIAGLIS 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. After waiting the required application time ensuring that the PLIAGLIS has dried, remove the peel by grasping a free-edge with your fingers and pulling it away from the skin. If the peel does not pull away freely, the cream may not be completely dried. If this occurs, use a gauze to wipe away any PLIAGLIS cream that has not dried. If skin irritation or a burning sensation occurs during application, remove PLIAGLIS immediately. If PLIAGLIS comes into contact with your eye, immediately rinse your eye with water or salt solution. Protect the eye and avoid rubbing until feeling returns.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 (light-headedness, 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.

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.

Methemoglobinemia:
Mild methemoglobinemia is characterized by tissue cyanosis, a bluish-grey or brownish discoloration of the skin, especially around the lips and nail beds, which is not reversed by breathing 100% oxygen. Clinical signs may also include pallor and marbleization.

Severe methemoglobinemia (MetHb concentrations above approximately 25%) is associated with signs of hypoxemia, ie. dyspnea, tachycardia and depression of consciousness.

Drug-induced methemoglobinemia may occur with the use of drugs including but not limited to sulfonamides, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates

and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine and quinine.

Acetaminophen has been shown to induce methemoglobin formation *in vitro* and in animals. In humans, methemoglobin formation is very rare at therapeutic doses and overdoses of acetaminophen.

It should be kept in mind that PLIAGLIS is contraindicated for patients with congenital or idiopathic methemoglobinemia. Patients with glucose-6-phosphate dehydrogenase deficiency are more susceptible to drug-induced methemoglobinemia (see also CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PLIAGLIS (lidocaine 7% and tetracaine 7%) cream is an emulsion in which the oil phase is a 1:1 eutectic mixture of lidocaine 7 % and tetracaine 7 %. 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 resulting in local anesthesia. When applied to intact skin, PLIAGLIS provides local dermal analgesia by the release of lidocaine and tetracaine from the cream into the skin. The migration into the epidermal and dermal layers of the skin, followed by accumulation in the vicinity of dermal pain receptors and nerve endings stabilizes the neuronal membrane and prevents nerve impulse initiation and conduction, thereby effecting local anaesthetic action. The depth of dermal analgesia depends upon the application time and the applied dose.

Pharmacodynamics

Duration of Analgesia: Duration of analgesia was evaluated using a pinprick test in 40 adult volunteers. The mean and median duration of analgesia was shown to be 9.4 and 11 hours, respectively, with a minimum duration of 2 hours while 55% of PLIAGLIS treated subjects still reported diminished sensation at the end of the 13-hour study period. There was no difference between the 30-minute and 60-minute PLIAGLIS application periods with respect to the mean for time to return of sensation.

Pharmacokinetics

Absorption:
The amount of lidocaine and tetracaine systemically absorbed from
PLIAGLIS is directly related to both the duration of application and the surface area over which it is applied (Table 6). Application of 59 g of PLIAGLIS over 400 cm^2 for up to 120 minutes to adults produces peak plasma concentrations of lidocaine of 220 ng/mL, which is $1/20^{th}$ the lower limit of systemic toxic levels. Tetracaine plasma levels were not measurable (<0.9 ng/mL).

Systemic exposure to lidocaine, as measured by C_{max} and AUC_{0-24}, was proportional to the application area, and increased with application time up to 60 minutes. There was no significant difference between older subjects (≥ 65 years of age) and younger adults (18-64 years of age) in the pharmacokinetic parameters of lidocaine.

Table 6: Absorption of lidocaine and tetracaine following application of PLIAGLIS

PLIAGLIS (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 α-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.

Liver disease and heart failure patients showed reduced volume of distribution and plasma clearance for lidocaine. The lidocaine plasma clearance and volume of distribution was not abnormal in patients with renal disease.

Volume of distribution and protein binding has 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-de-ethylation to MEGX and GX, is primarily mediated by CYP1A2 with a minor role of CYP3A4. The metabolite, 2, 6-xylidine, has unknown pharmacologic activity.

Hydroxylation reactions are also involved in lidocaine metabolism producing 3-hydroxylidocaine, 3-hydroxy-MEGX and other metabolites. 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 non-specific cholinesterases, in the plasma and liver. The hydrolysis products are *p*-aminobenzoic acid and diethylaminoethanol, both of which have an unspecified activity.

Excretion:
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 8–10 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 and Conditions

Geriatrics:
After application of 31g of PLIAGLIS 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.

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.

STORAGE AND STABILITY

PLIAGLIS (lidocaine 7% and tetracaine 7%) cream should be stored in a refrigerator at 2-8°C. Protect from freezing.

SPECIAL HANDLING INSTRUCTIONS

Hands should be washed after handling PLIAGLIS (lidocaine 7% and tetracaine 7%) cream and eye contact with PLIAGLIS should be avoided. Access to PLIAGLIS by children or pets should be prevented during usage, disposal and storage of the product.

Upon removal from the treatment site, **discard used PLIAGLIS in a location that prevents accidental ingestion by children or pets.** Used PLIAGLIS tubes should be disposed of immediately.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PLIAGLIS (lidocaine 7% and tetracaine 7%) cream is available as a topical anesthetic cream.

Each gram of PLIAGLIS contains lidocaine (70 mg) and tetracaine (70 mg). The non-medicinal ingredients in PLIAGLIS are calcium hydrogen phosphate (anhydrous), purified water, polyvinyl alcohol, paraffin (white, soft), sorbitan monopalmitate, methylparaben, propylparaben.

PLIAGLIS is available in a 15 or 30 g laminate tube with a polypropylene cap.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

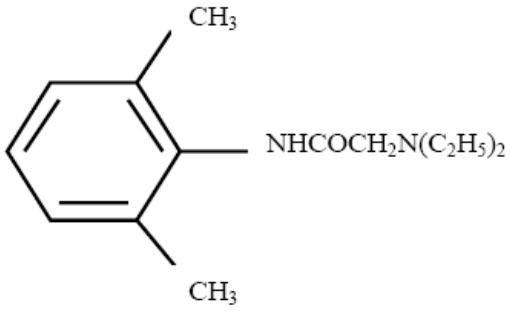
Drug Substance (Lidocaine)

Proper name: Lidocaine

Chemical name:
Acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-

Molecular formula and molecular mass:
$C_{14}H_{22}N_2O$, molecular weight: 234.3

Structural formula:



Physicochemical properties:
Lidocaine is a white or off-white crystalline powder that is very soluble in dichloromethane and in ethanol (96%), freely soluble in ether, and practically insoluble in water. The melting point of lidocaine is between 66-70°C.

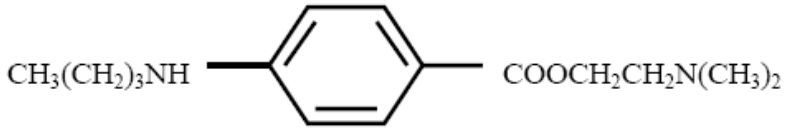
Drug Substance (Tetracaine)

Proper name: Tetracaine

Chemical name:
2-(Dimethylamino)ethyl 4(butylamino)benzoate

Molecular formula and molecular mass:
$C_{15}H_{24}N_2O_2$, molecular weight: 264.4

Structural formula:



Physicochemical properties:
Tetracaine is a white crystalline powder that is poorly soluble in water, and freely soluble in ethanol and isopropyl ether. The melting point of tetracaine is 41-46°C.

CLINICAL TRIALS

Study demographics and trial design:

In four clinical trials, adult subjects were treated with PLIAGLIS (lidocaine 7% and tetracaine 7%) cream and/or placebo prior to undergoing a superficial minor or major dermatologic procedure. Ninety-four percent (94%) of adults treated with PLIAGLIS and placebo were 18-64 years in age. For both the PLIAGLIS and placebo treated groups, 80% were females and 20% were males. All 6 skin types (Fitzpatrick classification scale) were represented with skin types II, III and IV the most common.

Three studies were double-blind, randomized, paired (within subject comparison), and placebo-controlled in which the subjects received a concurrent application of PLIAGLIS and placebo to the "top or right" and "bottom or left" sides of the treatment area, respectively (Studies SCP 40-05, SCP 41-05, SCP 43-05). A fourth study (Study SCP 42-05) employed a double-blind, randomized, parallel (between subjects comparison), and placebo-controlled design.

PLIAGLIS and/or placebo were applied for 20 or 30 minutes for dermal filler injection, pulsed dye laser therapy, and facial laser resurfacing. An application time of 60 minutes was employed for laser-assisted tattoo removal. Treatment with PLIAGLIS resulted in statistically significant less pain compared to placebo treatment, as measured by a 100 mm visual analog scale (VAS) Table 7). In addition, the secondary endpoint Investigator's evaluation of pain intensity and adequacy of anesthesia showed that the intensity of pain in patients in the PLIAGLIS group was lower than the placebo.

PLIAGLIS was well tolerated by patients receiving dermal procedures.

Study results:

The following table presents the primary endpoint, which is the subject pain evaluations measured as a mean VAS scale score (Table 7).

Table 7: Summary of subject pain evaluations in dermal procedures following application of PLIAGLIS versus Placebo

Study Code	SCP-40-05	SCP-41-05	SCP-42-05	SCP-43-05
Total No. of Patients (Pliaglis/Placebo)	N = 70 (70/70)	N = 54 (54/54)	N = 79 (42/37)	N = 62 (62/62)
Dermatologic Procedure	Dermal filler injections	Non-ablative laser facial resurfacing	Pulsed dye laser therapy	Laser-assisted tattoo removal
Application Period	30 min	30 min	20 min	60 min
Mean 100 mm Visual Analog Scale Score Pliaglis Placebo p-Value	 24.2 37.4 <0.0001[a]	 21.4 38 <0.0001[a]	 16.4 30.9 0.0008[b]	 39.1 58.6 <0.0001[a]

[a] paired t test; [b] two sample t test

In a trial of PLIAGLIS in pediatric patients aged 5-17 years undergoing venipuncture (blood draw or intravenous line placement), PLIAGLIS applied for 30 minutes failed to show efficacy over placebo in reducing the pain associated with the procedure.

DETAILED PHARMACOLOGY

After oral administration of 5 mg lidocaine to rats, the absolute bioavailability compared to the same dose administered intravenously was 16%. The low bioavailability is due to a high first-pass effect rather than any intrinsic limitation of absorption. In rats, the pharmacokinetic parameters of lidocaine were dose-proportional after intravenous administration of 2.5, 5 and 10 mg/kg. Studies in rats using iontophoresis and radioactive lidocaine showed that the main mechanism of clearance of lidocaine from the skin is through the skin microcirculation. With passive lidocaine application to the epidermis, there was direct penetration to the skin only. Percutaneous absorption of tetracaine has been demonstrated by efficacy of anesthesia, with the rate limiting step for absorption considered to be through the stratum corneum.

In vitro, 15 % of the administered lidocaine is bound to erythrocyte membranes and 61% is free in the cytosol. The binding of lidocaine, 1 μg/mL, to α_1-acid glycoprotein was 50%, compared to 64% in plasma. Addition of 2 mg/mL α_1-acid glycoprotein to plasma increased the binding of lidocaine to 86%, indicating a preferential binding of lidocaine to α_1-acid glycoprotein. There is no significant binding of lidocaine in the cerebrospinal fluid. Intravenous administration of radioactive [C^{14}] tetracaine, 2 mg/kg, to guinea pigs showed that initially, the concentration of radioactivity in the lung was at least 10-fold higher than the concentration in any of the other tissues or serum, which later subsided. At 90 minutes after injection, the only tissues with concentrations of radioactivity higher than the serum were the liver, kidneys and adrenals.

Studies in rats, guinea pigs, dogs and humans showed that lidocaine is metabolized by the CYP 450 enzymes. The following metabolites were present in all species: monoethylglycinexylidide

(MEGX, the product of a single deethylation of lidocaine), glycincexylidide (GX, the product of a second deethylation), 3-hydroxylidocaine (hydroxylation product), 3-hydroxymonoethylglycinexylidide (3-hydroxyMEGX, hydroxylation and deethylation product), and 2, 6-xylidine (hydrolysis of amide bond of MEGX). CYP3A4, is responsible for the formation of MEGX and CYP1A2 catalyzed the 3-hydroxylation of lidocaine in microsomes from both rats and humans.

Tetracaine has an ester bond that is hydrolysed by nonspecific cholinesterases that are present in the plasma and liver. The hydrolysis products are p-butylaminobenzoic acid and diethylaminoethanol. Due to the plasma hydrolysis, tetracaine is used for spinal anesthesia and topical local anesthesia.

The elimination of lidocaine has also been studied in a variety of animal species. The percentage of the dose excreted as unchanged lidocaine was 2.8% in humans, 2.0% in dogs and less than 1% in the other animals. For all species, greater than 65% of the dose was eliminated in the urine within 24 h and fecal excretion was much lower (< 1%).

Elimination of tetracaine in mice, rats, rabbits and horses showed that about 10% of the dose was present in the urine as tetracaine N-oxide, and less than 2% of the dose was present as unchanged tetracaine.

TOXICOLOGY

Acute Toxicity:

Three single dose toxicity studies were conducted using PLIAGLIS (lidocaine 7% and tetracaine 7%) cream to examine dermal absorption of the cream in rabbits and neonatal pigs. New Zealand White rabbits were exposed to PLIAGLIS (6g) for 2 hours. PLIAGLIS was minimally irritating to rabbits with no evidence of erythema with 72 hours of exposure. In another study, on New Zealand White rabbits, conducted with an earlier formulation of PLIAGLIS, a mild erythema was observed in 2 animals post 72 hours after exposure. Dermal absorption and dermal irritation studies were also conducted in male and female Landrace-Duroc Cross neonatal piglets exposed to 5 or 10g of PLIAGLIS for 30 and 60 minutes. All piglets survived the treatment period with no evidence of adverse clinical signs. No gross changes were observed at the site of application and, at histopathology, no dermal changes were noted.

Repeat Dose Toxicity:

No repeat dose toxicity studies have been performed on the PLIAGLIS formulation.

A 28-day repeat dose dermal toxicity study was conducted with a patch formulation containing a eutectic mixture of lidocaine 7% and tetracaine 7% in New Zealand White rabbits. Three active patches, 210 mg each of lidocaine and tetracaine in total, were applied to each animal for 2 hours per day. There was no evidence of systemic toxicity but local irritation was observed at the site of application. There was some evidence of storage depots in the skin, with later release into the systemic circulation. During the first week of treatment (2-3 applications at the same site),

minimal irritation was observed. Repeated treatment during Weeks 2 through 4 resulted in an increased incidence and severity of the irritation response as compared to Week 1. Histopathological evaluation revealed treatment-related changes in skin of all animals exposed to the patch. These changes included epidermal surface exudates, epidermal necrosis, acute dermatitis, trace or moderate epithelial hyperplasia, fibrosis and trace hyperkeratosis, for which there was no gender difference. In comparison, the placebo-patch sites showed no, or minimal, changes. Although this study represented a highly exaggerated (high dose exposure) and an unintended use (e.g., multiple use on the same site), the animals tolerated the repeated application of lidocaine and tetracaine reasonably well during the study.

Mutagenicity:
The mutagenicitity 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, with and without metabolic activation, 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 Bacterial Reverse Mutation 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. There was a weak increase in chromosomal aberrations in the presence of metabolic activation at the highest tested concentration of 300 µg/mL.

Carcinogenicity:
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of PLIAGLIS or its active ingredients, lidocaine or tetracaine.

Reproductive and Developmental Toxicity:
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 (1500 mg/m^2 or 2-fold higher than the single dermal administration [SDA]). Although lidocaine treatment of male rats increased the copulatory interval and led to dose-related decreases in homogenization resistant sperm head count, daily sperm production, and spermatogenic efficiency, the treatment did not affect overall fertility in male rats when given subcutaneous doses up to 60 mg/kg (360 mg/m^2 or <1-fold the SDA). Multiples of exposure is based on a SDA of 1 g of PLIAGLIS applied to 10 cm^2 for 60 minutes to a 60 kg person (645 mg/m^2).

Sprague-Dawley rats, treated via subcutaneous injections of tetracaine at doses up to 7.5 mg/kg (45 mg/m^2 or <1- fold the single dermal administration [SDA]) showed that tetracaine did not affect fertility in male or female rats. The No-observed-effect-level (NOEL) for developmental effects was 7.5 mg/kg/day and the NOEL for parental toxicity was 2.5 mg/kg/day.

Teratogenic Effects: Lidocaine was not teratogenic in Sprague-Dawley rats at doses up to 60 mg/kg (360 mg/m^2 or <1-fold the SDA), nor in rabbits at doses up to 15 mg/kg (180 mg/m^2 or <1-fold the SDA). Tetracaine was not teratogenic in rats given subcutaneous doses up to 10 mg/kg (60 mg/m^2), nor in rabbits at doses up to 5 mg/kg (60 mg/m^2 or <1-fold the SDA). A 1:1

eutectic mixture of lidocaine and tetracaine injected subcutaneously, was not teratogenic in rats (60 mg/m^2 or <1-fold the SDA) or rabbits (120 mg/m^2 or <1-fold the SDA).

Nonteratogenic Effects: Lidocaine containing 1:100,000 epinephrine at a dose of 6 mg/kg (<1-fold the SDA) injected into the masseter muscle of the jaw or into the gum of the lower jaw of Long-Evans hooded pregnant rats on gestation Day 11, lead to developmental delays in neonatal behaviour 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 postnatal maturational, behavioural, or reproductive development was not affected by maternal subcutaneous administration of tetracaine during gestation and lactation up to doses of 7.5 mg/kg (45 mg/m2 or <1-fold the SDA).

No adequate and well-controlled studies have been conducted in pregnant women. Because animal studies are not always predictive of human response, PLIAGLIS should be used during pregnancy only if the potential benefit justifies risk to the fetus. (see WARNINGS AND PRECAUTIONS, Special Populations)

REFERENCES

Barat S, Abdel-Rahman M. Cocaine and lidocaine in combination are synergistic convulsants. Brain Res 1996; 742:157-62.

Bargetzi MJ, Aoyama T, Gonzalez FJ, Meyer, UA. Lidocaine metabolism in human liver microsomes by cytochrome P450IIIA4. Clin Pharmacol Ther 1989; (46):521-27.

Bennett PN, Aarons LJ, Bending MR, Steiner JA, Rowland M. Pharmacokinetics of lidocaine and its deethylated metabolite: Dose and time dependency studies in man. J Pharmacokin Biopharm 1982; 10(3):265-81.

Bryan HA, Alster TS. The S-Caine peel: a novel topical anesthetic for cutaneous laser surgery. Dermatol Surg 2002; 28 (11): 999-1003.

Chen JZ, Alexiades-Armenakas MR, Bernstein LJ, Jacobson LG, Friedman PM, Geronemus RG. Two randomized, double-blind, placebo-controlled studies evaluating the S-Caine Peel for induction of local anesthesia before long-pulsed Nd: YAG laser therapy for leg veins. Dermatol Surg 2003; 29 (10):1012-8.

Chen JZ, Jacobson LG, Bakus AD, Garden JM, Yaghmai D, Bernstein LJ, et al. Evaluation of the S-Caine peel for induction of local anesthesia for laser-assisted tattoo removal: randomized, double-blind, placebo-controlled, multicenter study. Dermatol Surg 2005; 31 (3):281-6.

Conrad KA, Byers JM, Finley PR, Burnham L. Lidocaine elimination: effects of metoprolol and of propranolol. Clin Pharmacol Ther 1983; 33(2):133-8.

de Leede LGJ, de Boer AG, Roozen CPJM, Breimer DD. Avoidance of "first-pass" elimination of rectally administered lidocaine in relation to the site of absorption in rats. JPharmacol Exp Ther 1983 ; (255):181-5.

Derlet RW, Albertson TE, Tharratt RS. Lidocaine potentiation of cocaine toxicity. Ann Emerg Med 1991; 20(2):135-8.

Feely J, Wilkinson GR, McAllister CB, Wood AJJ. Increased toxicity and reduced clearance of lidocaine by cimetidine. Ann Intern Med 1982; 96(5):592-94.

Foldes FF. The influence of metabolic transformation on the toxicity of local anesthetic agents in man. Acta Anaesthesiol Scand Suppl 1966; 23: 591-7.

Fujinaga M, Mazze RI. Reproductive and teratogenic effects of lidocaine in Sprague-Dawley rats. Anesthesiol 1986; 65:626-632.

Hansen D. Distribution and metabolism of 14C-tetracaine after intravenous injection in guinea pig. Nauyn-Schmiedebergs Arch Pharmak 1970 ;(265):347-58.

Holley FO, Ponganis KV, Stanski DR.Effects of cardiac surgery with cardiopulmonary bypass on lidocaine disposition. Clin Pharmacol Ther 1984; 35(5):617-26.

Imaoka S, Enomoto K, Oda Y, Asada A, Fujimori M, Shimada T et al. Lidocaine metabolism by human cytochrome P-450s purified from hepatic microsomes: comparison of those with rat hepatic cytochrome P-450s. J Pharmacol Exp Ther 1990; (255):1385-91.

Jih MH, Friedman PM, Sadick N, Marquez DK, Kimyai-Asadi A, Goldberg LH. 60-minute application of S-Caine Peel prior to 1,064 nm long-pulsed Nd: YAG laser treatment of leg veins. Lasers Surg Med 2004; 34: 446-50.

Keenaghan JB, Boyes RN. The tissue distribution, metabolism and excretion of lidocaine in rats, guinea pigs, dogs and man. J Pharmacol Exp Ther 1972 ;(180):454-63.

Ke J, Tam YK, Koo WWK, Coutts RT, Finegan BA.Lack of acute effect on lidocaine pharmacokinetics from parenteral nutrition. Ther Drug Monit 1990; 12(2):157-62.

Lai PM, Anissimov YG, Roberts MS. Lateral iontophoretic solute transport in skin. Pharmaceutical Research 1999 ;(16):46-54.

Mazumdar B, Tomlinson AA, Faulder GC. Preliminary study to assay plasma amethocaine concentrations after topical application of a new local anaesthetic cream containing amethocaine. Br J Anaesth 1991; 67:431-6.

McCafferty, D.F., et al., Comparative in vivo and in vitro assessment of the percutaneous absorption of local anaesthetics. Br J Anaesth 1988; 60(1): p. 64-9.

McCafferty DF, Woolfson AD, Boston V. In vivo assessment of percutaneous local anaesthetic preparations. Br J Anaesth 1989; 62(1):17-21.

Michalets EL. Update: clinically significant cytochrome P-450 drug interactions. Pharmacotherapy, 1998; 18(1): p. 84-112.

Mihaly GW, Moore RG, Thomas J, Triggs EJ, Thomas D, Shanks CA. The pharmacokinetics and metabolism of the anilide local anaesthetics in neonates. I. Lignocaine. Eur J Clin Pharmacol 1978;13:143-52.

Mofenson HC, Caraccio TR, Greensher J.Lidocaine toxicity from topical mucosal application. With a review of the clinical pharmacology of lidocaine. Clin Pediatr 1983; 22(3):190-2.

Momose A, Fukuda J. A new metabolite of tetracaine. Chem Pharm Bull 1976; (24):1637-40.

Patel D, Chopra S, Berman MD. Serious systemic toxicity resulting from use of tetracaine for pharyngeal anesthesia in upper endoscopic procedures. Dig Dis Sci 1989; 34(6):882-84.

Piafsky KM, Knoppert D. Binding of local anesthetics to alpha1-acid glycoprotein. Clin Res 1979; 26:836A.

Roden D. Antiarrhythmic Drugs In: J. Hardman et al., editors. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, New York: McGraw-Hill:1996; 839-874.

Siegmund JB, Wilson JM, Imhof TE. Amiodarone interaction with lidocaine. J Cardiovasc Pharmacol 1993; 21(4):513-35.

Singh P, Roberts MS. lontophoretic transdermal delivery of salicylic acid and lidocaine to local subcutaneous structures. J Pharm Sci 1993; 82:127-131.

Smith RF, Kurkjian MF, Mattran KM, Kurtz SL. Behavioral effects of prenatal exposure to lidocaine in the rat: Effects of dosage and of gestational age at administration. Neurotoxicol Teratol 1989; 11:395-403.

Supradist S, Notarianni LJ, Bennett PN. Lignocaine kinetics in the rat. J Pharm Pharmacol 1984; 36:240-243.

Thomson PD, Melmon KL, Richardson JA, Cohn K, Steinbrunn W, Cudihee R. et al. Lidocaine pharmacokinetics in advanced heart failure, liver disease, and renal failure in humans. Ann Int Med 1973; 78:499-508.

Tucker GT, Boyes RN, Bridenbaugh PO, Moore DC. Binding of anilide-type local anesthetics in human plasma: II. Implications in vivo, with special reference to transplacental distribution. Anesthesiol 1970; 33:287-303.

Woolfson AD, McCaffety DF, McClelland KH, Boston V. Concentration-response analysis of percutaneous local anaesthetic formulations. Br J Anaesth 1988; 61:589-9

PART III: CONSUMER INFORMATION

PrPLIAGLIS™
Lidocaine and Tetracaine Cream

This leaflet is part III of a three-part "Product Monograph" published when PLIAGLIS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PLIAGLIS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
PLIAGLIS is used in adults on healthy, unbroken skin to reduce pain prior to skin-related procedures such as:

Less painful procedures:
- collagen injections
- laser facial resurfacing
- pulsed dye laser therapy
- laser-assisted hair removal
- having an intravenous line started or when having a blood test

More painful procedures:
- laser-assisted tattoo removal
- laser leg vein treatment

What it does:
PLIAGLIS blocks skin nerve reactions. You therefore feel less pain.

When it should not be used:
You should not use PLIAGLIS:
- on an area larger than the area covered by two standard postcards
- for any longer than 60 minutes
- if you have methemoglobinemia (a blood disorder)
- if you are allergic to:
    - lidocaine
    - tetracaine
    - local anesthetics of the amide or ester type
    - Para-aminobenzoic acid (PABA)
    - any other component of the product

What the medicinal ingredients are:
lidocaine and tetracaine

What the nonmedicinal ingredients are:
calcium hydrogen phosphate (anhydrous), methylparaben, paraffin (white, soft), polyvinyl alcohol, propylparaben, purified water, sorbitan monopalmitate

What dosage forms it comes in:
PLIAGLIS is available as a cream (lidocaine 7% and tetracaine 7%) in a 15 or 30 g tube.

WARNINGS AND PRECAUTIONS

For external use only. Not for home use by patient. Only for use in clinical settings.

PLIAGLIS should not be applied to open wounds, irritated skin, mucous membranes including; mouth, lips, nose, eyes, ears, genital or anal areas.

BEFORE you use PLIAGLIS talk to your doctor or pharmacist if you:
- are currently using other products that contain local anaesthetic or that numb the skin.
- have an infection, skin rash or cut at, or near, the area where you want to apply PLIAGLIS
- have dermatitis or any other skin problems or disease
- suffer from liver, kidney or heart problems or any other illness or disease
- have glucose-6-phosphate dehydrogenase deficiency
- are pregnant or trying to get pregnant
- are breastfeeding. PLIAGLIS should not be applied to the breasts of breastfeeding women
- are less than 18 or over 65 years of age.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with PLIAGLIS:
- heart medications such as quinidine, disopyramide, tocainide, mexiletine, amidarone
- drugs known to induce the blood disorder 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.
- other local anesthetic drugs
- aminosalicylic acid
- suxamethonium (succinylcholine)
- HIV protease inhibitors, macrolides, azole antifungals, and cimetidine
- antimyasthenics, cyclophosphamide, echothiophate, isoflurophate, and thiopeta.

PROPER USE OF THIS MEDICATION

PLIAGLIS should be used in the treatment location where the procedure will be performed.

Use PLIAGLIS exactly as prescribed.

If PLIAGLIS comes into contact with your eye, immediately

rinse your eye with water or salt solution. Protect the eye and avoid rubbing until feeling returns.

Do not reapply to treated area after the procedure. If your procedure has to be repeated, the treated area must have time to fully recover before using PLIAGLIS again.

PLIAGLIS is not to be used before or after vaccinations.

Usual adult dose:
PLIAGLIS should only be applied to dry, healthy, unbroken skin.

PLIAGLIS should be spread evenly and thinly (approximately 1 mm thickness) with a metal spatula or tongue depressor across the area to be treated (as determined by your doctor). Do not touch PLIAGLIS with your fingers or cover the treated area. Do not rub PLIAGLIS into the skin. PLIAGLIS should be applied only once per procedure.

The amount of PLIAGLIS that should be used is determined by the size of the area to be treated and will be determined by your doctor.

Area to be treated	**Amount of PLIAGLIS dispensed by length (cm)**	**Amount of PLIAGLIS by weight (g)**
Approximately the size of a two dollar coin ("toonie").	3	1.3
Approximately the size of a credit card.	12	5
Approximately the size of two credit cards.	24	11
Approximately the size of a standard postcard.	61	26 (one 30 g tube)
The area treated should be no bigger than 400cm^2 or approximately the size of two postcards	121	52 (two 30 g tubes)

Less painful procedures:
- The cream must be left to dry for no longer than 20-30 minutes prior to the procedure.

More painful procedures:
- The cream must be left to dry for no longer than 60 minutes prior to the procedure.

After waiting for the required application time the dried cream will have formed a soft peel on your skin. Prior to the procedure, PLIAGLIS must be removed by grasping a free-edge of the peel and pulling it away from the skin.

The peel must be carefully disposed of immediately after removal out of reach and site of children and pets. Even dried PLIAGLIS removed after use may contain a large amount of medicine that could cause serious injury to a pet or small child if chewed on or eaten.

Wipe with a compress any remaining peel residue from the area.

Hands should be washed immediately after removing and disposal of the peel.

Once PLIAGLIS has been removed, your skin will feel numb. Take care not to scratch or rub the numbed area or touch very hot or cold surfaces until the numbness has stopped as you could accidently damage the skin.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:
- headache
- vomiting
- dizziness
- fever
- sore throat (pharyngitis)
- sweating
- tingling in the arms and/or legs (parasthesia)

During or immediately after treatment with PLIAGLIS, the skin at the site of treatment may develop:
- redness, discolouration, paleness
- swelling (including the face and eyelid)
- itching, pain, irritation, tingling, burning sensation
- peeling

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		**Talk with your doctor or pharmacist**		**Remove PLIAGLIS and seek immediate medical help**
		Only if severe	**In all cases**	
Very rare	**Allergic reaction:** skin rash, hives, itching or swelling, difficulty swallowing or breathing			✓

This is not a complete list of side effects. For any unexpected effects while taking PLIAGLIS, contact your doctor or pharmacist.

HOW TO STORE IT

Store in a refrigerator, temperature 2-8°C. Protect from freezing.

Keep out of reach and sight of children.

Access to PLIAGLIS by children or pets should be prevented during use, disposal and storage of the product.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.galderma.ca
or by contacting the sponsor, Galderma Canada, at:
1-800-467-2081

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