Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pliaglis 70mg/g + 70mg/g cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 gram of cream contains 70 mg lidocaine and 70 mg tetracaine.
Excipients with known effect:
methyl parahydroxybenzoate (E218) 0.5 mg/g
propyl parahydroxybenzoate (E216) 0.1 mg/g
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream
White to off-white viscous cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pliaglis is indicated in adults to produce local dermal anaesthesia on intact skin prior to dermatological procedures.

4.2 Posology and method of administration

Posology
For use in adults and elderly:
For dermatological procedures such as pulsed-dye laser therapy, laser-assisted hair removal, non-ablative laser facial resurfacing, dermal filler injections and vascular access, Pliaglis should be applied onto intact skin at a thickness of approximately 1mm for 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 dermatological procedures such as laser-assisted tattoo removal, and laser leg vein ablation, Pliaglis should be applied onto intact skin at a thickness of approximately 1mm 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.

Surface Area of Treatment Site (cm2)	Approximate weight of Pliaglis Dispensed (g)	
10	1.3	2 fingertip units
50	6.5	Half content of a 15g tube
100	13	Full content of a 15g tube
200	26	Full content of a 30g tube
400	52	Full content of two 30g tubes

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

Hepatic, renal and cardiac impairment
Pliaglis should be used with caution in patients with hepatic, renal and cardiac impairment (see section 4.4).

Paediatric population
The safety and efficacy of Pliaglis in children and adolescents aged up to 18 years have not been established. Therefore, the use of Pliaglis is not recommended in children and adolescents.

Method of administration
Pliaglis is for single patient use.
Cutaneous use only.

Precautions to be taken before handling or administering the medicinal product
For facial procedures, Pliaglis should be applied by healthcare professionals. For procedures on any other part of the body, Pliaglis should be applied by healthcare professionals or by patients adequately instructed in appropriate application technique.

Patients and healthcare professionals are recommended to avoid direct contact with the cream or the skin covered with the cream in order to prevent contact dermatitis.

Pliaglis should never be applied with fingers.
Pliaglis should only be applied with a flat surfaced tool such as a spatula or tongue depressor.
Hands should be washed immediately after removing and disposal of the peel.
For further instructions on handling and disposal of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to lidocaine, tetracaine, other anaesthetics of the amide or ester type, to para-aminobenzoic acid (a known by-product of tetracaine metabolism), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) or to any of the other excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

Contact with eyes should be avoided. Severe corneal lesions were observed in animal testing of similar products. Pliaglis should be used with caution in the proximity of the eyes. 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.
Any remaining peel residue should be carefully wiped with a compress after removing Pliaglis peel.
The treated area should not be occluded before removing Pliaglis from the skin.
Pliaglis should not be applied for a longer time than recommended in section 4.2.
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. See section 4.8.
Several local anaesthetics, including tetracaine, have been associated with methemoglobinemia. The risk of methemoglobinemia is greatest for patients with congenital or idiopathic 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.
Lidocaine has been shown to inhibit viral and bacterial growth. The effect of lidocaine and tetracaine cream on intradermal injections of live vaccines has not been determined. Therefore, it is not recommended to use it before injection of live vaccines.
Pliaglis should be used with caution in patients with hepatic, renal or cardiac impairment, and in subjects with increased sensitivity to systemic circulatory effects of lidocaine and tetracaine, such as the acutely ill or debilitated.
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.
Pliaglis contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216), which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The risk of additional systemic toxicity should be considered when Pliaglis is applied to patients receiving Class I antiarrhythmic medicinal products (such as quinidine, disopyramide, tocainide and mexiletine) and class III antiarrhythmic medicinal products (e.g. amiodarone) or other products containing local anaesthetic agents. Interactions following appropriate use of Pliaglis are unlikely since only low concentrations of lidocaine and tetracaine are found in the plasma after topical administration of Pliaglis recommended doses (see section 5.2).

Patients taking drugs associated with drug-induced methemoglobinemia such as fonamides, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, and quinine are at greater risk for developing methemoglobinemia.

Should Pliaglis be used concomitantly with other products containing lidocaine and/or tetracaine, cumulative doses from all formulations must be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of Pliaglis during pregnancy. Animal studies do not indicate direct or indirect harmful effects of tetracaine with respect to reproductive toxicity. Animal studies are insufficient for lidocaine with respect to reproductive toxicity (see section 5.3). Caution should be exercised when used in pregnant women.

Breastfeeding
Lidocaine and tetracaine are excreted in human milk, but at the recommended doses of Pliaglis, only low effects on breastfed newborns/infants are anticipated.
Therefore, Pliaglis can be used during breast-feeding as long as Pliaglis is not applied to the breast.

Fertility
There are no fertility data for the use of lidocaine and tetracaine in humans.
Lidocaine and tetracaine were not shown to alter fertility in animal studies.

4.7 Effects on ability to drive and use machines

No studies on the effects of Pliaglis on the ability to drive and use machines have been performed.
Pliaglis has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Localized skin reactions at the application site were very common adverse events in clinical studies with Pliaglis but were generally mild and transient in nature. Undesirable effects listed below include both treatment related adverse events and erythema, skin oedema and skin discoloration assessed on skin reaction evaluation scales. The application site adverse reactions that occurred in more than 10% of patients were erythema and skin discoloration. Skin oedema was a common adverse reaction. All other adverse reactions occurred in less than 1% of patients.

The adverse reactions, presented in the table below, are classified by System Organ Class and frequency, using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Most of the adverse reactions mentioned in the table below occurred at the application site of the cream.

System Organ Class	**Adverse Reactions, including local tolerance signs**				
	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
Nervous System Disorders				Paresthesia	
Eye Disorders				Eyelid oedema	
Skin and Subcutaneous Tissue Disorders	Erythema Skin discolouration	Skin oedema	Pruritus Pain of skin	Pallor Skin burning sensation Swelling face Skin exfoliation Skin irritation	Urticaria
General Disorders and Administration			Pain		

Site Conditions					

Rare allergic or anaphylactoid reactions associated with lidocaine and tetracaine or other ingredients in Pliaglis can occur. See section 4.4.
Systemic adverse reactions following appropriate use of Pliaglis are unlikely due to the small doses of lidocaine and tetracaine that are absorbed (see section 5.2).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Overdose with Pliaglis is unlikely but signs of systemic toxicity will be similar in nature to those observed after administration of other local anaesthetics, i.e., excitatory CNS symptoms and, in severe cases, CNS depression and myocardial depression.
If overdose occurs, patients must be placed under close observation. Severe neurological symptoms (seizures, CNS depression) may start at plasma concentration of lidocaine as low as 1000 ng/mL. Toxic levels of lidocaine (>5000ng/mL) cause CNS toxicity, including risk of seizure. Signs of overdose require symptomatic treatment such as assisted ventilation and spasmolytic agents. Dialysis is of negligible value in the treatment of acute overdosage of lidocaine or tetracaine. Due to slow systemic absorption, a patient with symptoms of toxicity should be observed for several hours following any treatment of these symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:anaesthetics, local; amides
ATC code: N01BB52

Mechanism of action
Pliaglis provides local dermal anaesthesia when applied to intact skin by the release of lidocaine and tetracaine into the epidermal and dermal layers of the skin with the accumulation of lidocaine and tetracaine in the area of dermal pain receptors and nerve endings. Both lidocaine and tetracaine block sodium ion channels required for the initiation and conduction of impulses, resulting in local anaesthesia. The degree of anaesthesia depends on the application time.

Pharmacodynamic effects
In a clinical pharmacodynamic study (pinprick test, N=40), the mean and median duration of anaesthesia were shown to be 9.4 and 11 hours, respectively, with a minimum duration of 2 hours and a maximum estimated duration of 13 hours.

Clinical efficacy and safety
The efficacy and safety of Pliaglis were evaluated in 12 Phase III, randomized, double-blind, placebo-controlled clinical studies including a total of 669 adult patients, before various dermatologic procedures.
Pliaglis and placebo were applied on 2 comparable treatment areas for 30 minutes for dermatological procedures including dermal filler injection, laser-assisted hair removal, non-ablative laser resurfacing, pulse-dyed laser therapy (2 studies with 20 min application) and for vascular access. The cream was applied for 60 minutes for laser-assisted tattoo removal, and laser ablation for leg veins. Treatment with Pliaglis resulted in statistically significantly less pain compared to placebo treatment in each study, as measured by a 100 mm Visual Analog Scale (VAS) evaluated by the subjects, except study 1 vascular access for which efficacy of Pliaglis was not demonstrated.

Table 1: Summary of phase III clinical studies for Pliaglis

Dermatologic Procedure	Number of patients	Pliaglis mean VAS (mm)	Placebo mean VAS (mm)	P-value (Pliaglis vs. placebo)
20 or 30 Min Application				
Pulsed Dye Laser Therapy (20', study 1)	80	16	31	P<0.001

Pulsed Dye Laser Therapy (20', study 2)	60	16	36	P<0.001
Laser-Assisted Hair Removal (30')	50	23	32	P=0.017
Non-Ablative Laser Resurfacing (30',study 1)	54	21	38	P<0.0001
Non-Ablative Laser Resurfacing (30',study 2)	40	31	55	P<0.001
Dermal Filler Injections (30')	70	24	37	P<0.0001
Collagen Injections (30')	52	23	40	P<0.001
Vascular access (study 1)	55	30	32	P=0.691
Vascular access (study 2)	55	16	30	P=0.004
60 Min Application				
Laser-Assisted Tattoo Removal (study 1)	30	43	66	P=0.001
Laser-Assisted Tattoo Removal (study 2)	63	39	59	P<0.0001
Laser-Assisted Leg Vein Ablation	60	27	43	P<0.001

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Pliaglis in all subsets of the paediatric population in local anaesthesia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption:
The systemic exposure of the two active substances depends on the dose, the duration of the application, the thickness of the skin (varying between different parts of the body) and the skin condition.

In adults, application of 59g of Pliaglis over 400 cm2 for up to 120 minutes produces a mean peak plasma concentration of lidocaine of 139ng/ml with a maximal peak plasma concentration of 220ng/ml. Systemic exposure to lidocaine, as measured by C_{max} and AUC_{0-24} was proportional to application area, and increased with application time up to 60 minutes. C_{max} was proportional to the percent of body surface area covered, with 2.5% coverage (400 cm^2) for 30 minutes producing maximum lidocaine concentration of approximately 60ng/ml. Tetracaine plasma levels were not measurable (<0.9ng/ml) in adults.

Distribution:
Following intravenous administration to healthy volunteers, the steady-state volume of distribution is approximately 0.8 to 1.3 l/kg. Approximately 75% of lidocaine is bound to plasma proteins (primarily alpha-1-acid glycoprotein). The volumes of distribution and protein binding have not been determined for tetracaine due to its rapid hydrolysis in plasma.

Biotransformation and Elimination:
Lidocaine is mainly eliminated by metabolism. Conversion to monoethylglycinexylidide (MEGX) and further to glycinexylidide (GX) is mediated predominantly by CYP1A2 and to a lesser extent by CYP3A4. MEGX is also metabolised to 2,6-xylidine. 2,6-xylidine is further metabolised by CYP2A6 to 4-hydroxy-2,6-xylidine that constitutes the main metabolite in urine (80%) and is excreted as conjugate. MEGX has a pharmacological activity similar to lidocaine while GX has less pharmacological activity.

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

The extent to which lidocaine and tetracaine are metabolised in the skin is not known. 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.

The mean elimination half-life of lidocaine from plasma after intravenous administration is approximately 1.8 hours. The mean elimination half-life of lidocaine from plasma after 30 min topical application of 9g (200cm^2) of Pliaglis is up to 12.1 hours

indicating a depot of lidocaine in the skin with subsequent release of drug to the systemic circulation. The half-life and clearance for tetracaine has not been established for humans, but hydrolysis in plasma is rapid.

Elderly
After application of 31g of Pliaglis over 400cm2 for 60 minutes (n=12), mean peak plasma levels of lidocaine were 48ng/ml for elderly patients (65 - 78 years of age). 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 in individuals with cardiac, renal or hepatic impairment. 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 its rapid hydrolysis in the plasma.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Reproductive toxicology
Lidocaine: No effects on male and female fertility were observed in rats. In studies of embryo/foetal development in rats and rabbits with dosing during organogenesis, no teratogenic effects were observed. However, animal studies are incomplete with respect to effects on pregnancy, parturition or postnatal development.
Tetracaine: No effects on fertility were observed in rats. In studies of embryo/foetal development in rats and rabbits with dosing during organogenesis, no teratogenic effects were observed. No effects were observed in the offspring of rats treated with a maternally toxic dose during late pregnancy and lactation. As there are no data for systemic exposure in rats, no comparison with exposure in humans can be made.
Lidocaine and tetracaine: In studies of embryo/foetal development with dosing during organogenesis, no teratogenic effects were observed.

Genotoxicity and carcinogenicity
Genotoxicity studies for lidocaine and tetracaine were negative. The carcinogenicity of lidocaine and tetracaine has not been studied. The lidocaine metabolite 2,6-xylidine has genotoxic potential in vitro. In a carcinogenicity study in rats with exposure to 2,6 xylidine in utero and postnatally and throughout their lifetime, tumours in the nasal cavity, the subcutis and the liver were seen. The clinical relevance of the tumour findings in short-term/intermittent/topical use of lidocaine is unknown. Taken into consideration the short treatment duration with Pliaglis, carcinogenic effects are not anticipated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate, anhydrous
Purified water,
Polyvinyl alcohol
Paraffin, white soft
Sorbitan monopalmitate
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C), including after opening.
Do not freeze.
Once opened, it should be used within 3 months. It is recommended that the date of opening is noted on the packaging.

6.5 Nature and contents of container

Laminated tube with a HDPE head and a polypropylene screw cap.
Tubes contain 15g or 30g.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Croma-Pharma GmbH
Industriezeile 6
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8 MARKETING AUTHORISATION NUMBER

PA0846/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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