PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

AMETOP® GEL 4%

Tetracaine (as tetracaine hydrochloride)

Gel, Tetracaine 4% w/w, for topical administration

Topical Analgesic

Valeo Pharma Inc.
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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS	04/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

AMETOP Gel 4% *(*Tetracaine Hydrochloride Gel) is indicated for:

- Percutaneous local anaesthetic to produce anaesthesia of the skin prior to venepuncture or venous cannulation, including intravenous injections of medications.

1.1 Pediatrics

Pediatrics (older than one month and in the case of premature babies: 1 month after the expected delivery date (44 gestation weeks) – 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of AMETOP Gel 4% in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness. There is no significant difference in pseudocholinesterase activity in men between the ages of 16 – 94 years and women aged 40 – 99years.

2 CONTRAINDICATIONS

AMETOP Gel 4% (Tetracaine Hydrochloride Gel) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patient who are hypersensitive to local anaesthetics of the ester type.
- Premature babies or full-term infants less than one month of age, in whom the metabolic pathway for tetracaine may not be fully developed. **For premature babies use of AMETOP Gel 4% is not recommended before 1 month after the expected delivery date (44 weeks gestation).**
- Do not apply AMETOP Gel 4% to broken skin, mucous membranes or to the eyes or ears.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

- **Adults (including the elderly):** No more than the contents of 1 tube (approximately 1g) should be applied per site of venepuncture or venous cannulation. In certain circumstances anaesthesia of more than one site may be necessary (e.g., where cannulation is difficult). In such cases, a maximum of 5 sites may be anaesthetized at the outset of a course of treatment, if required to ensure that a series of sites are available for cannulation in the event that venous access cannot be achieved at the first site. The maximum cumulative dose in a 24-hour period should not exceed 7 tubes.

- **Children (over 1 month of age):** The contents of no more than 1 tube (approximately 1 g) can be applied at separate sites in a single application. The maximum cumulative dose in a 24-hour period should not exceed 2 tubes.

4.4 Administration

Apply the contents of the tube to the skin starting from the centre of the area to be anaesthetised and cover with an occlusive dressing. The contents expellable from one tube (approximately one gram) are sufficient to cover and anaesthetise an area of up to 30 cm^2 (6 x 5 cm). Smaller areas of anaesthetised skin may be adequate in infants and small children. Each tube is intended for use on a single occasion only.

Adequate anaesthesia can usually be achieved for venepuncture following a thirty-minute application time, and for venous cannulation following a forty-five-minute application time; after which the gel should be removed with a gauze swab and the site prepared with an antiseptic wipe in the normal manner.

It is not necessary to apply AMETOP Gel 4% for longer than the above recommended times and anaesthesia is maintained for 4 to 6 hours in most patients after a single application.

5 OVERDOSAGE

Overdosage with AMETOP Gel 4% (Tetracaine Hydrochloride Gel) is unlikely to result from application to intact skin. If accidentally ingested systemic toxicity may occur, and signs will be similar to those observed after administration of other local anaesthetics.

Systemic effects of overdose of tetracaine have been described as: signs of inebriation, tingling, numbness of the tongue, tinnitus, nystagmus, nausea or vomiting, twitching and ultimately convulsions. Oxygen is recommended as the first line treatment for systemic toxicity.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	Gel / 4% w/w / Tetracaine hydrochloride	Potassium phosphate, purified water, sodium chloride, sodium hydroxide, sodium methylparaben, sodium propylparaben and xanthan gum

Description

1.5g internally lacquered, aluminum collapsible tubes, designed to deliver 1.0 g of AMETOP Gel 4% (Tetracaine Hydrochloride Gel) on squeezing.

7 WARNINGS AND PRECAUTIONS

General

Only apply to intact, unbroken skin. Not to be taken internally.

Repeated exposure to AMETOP Gel 4% (Tetracaine Hydrochloride Gel) may increase the risk of sensitisation reactions to tetracaine.

Do not use AMETOP Gel 4% to anaesthetize skin prior to immunization. (See 9.4 Drug-Drug Interactions).

Ear/Nose/Throat

Do not apply AMETOP Gel 4% to broken skin, mucous membranes or to the eyes or middle ear. AMETOP Gel 4%, like other local anaesthetics may be ototoxic and should not be instilled into the middle ear or used for procedures which might involve penetration into the middle ear.

Immune

AMETOP Gel 4% contains sodium methylparaben and sodium propylparaben which may cause allergic reactions (possibly delayed).

Neurologic

Although the systemic availability of tetracaine by percutaneous absorption of AMETOP Gel 4% is low, caution should be exercised in patients with epilepsy.

Reproductive Health: Female and Male Potential

Fertility

No studies have been conducted to determine if tetracaine hydrochloride has an effect on fertility.

7.1 Special Populations

7.1.1 Pregnant Women

The product is not recommended for use by pregnant women. The rapid hydrolysis of tetracaine by plasma pseudocholinesterase suggests that it is unlikely to present a significant hazard to the foetus when used as indicated.

7.1.2 Breast-feeding

It is not known whether tetracaine or its metabolite are secreted in breast milk. Therefore the product Is not recommended for use in breastfeeding mothers.

7.1.3 Pediatrics

Pediatrics (premature babies): Use of AMETOP Gel 4% in premature babies before 1 month after the expected delivery date (44 weeks gestation) and in full term infants less than one month of age is not recommended because the metabolic pathway for tetracaine may not be fully developed.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Slight erythema is frequently seen at the site of application and is due to the pharmacological action of tetracaine dilating capillary vessels. This may help in delineating the anaesthetised area.

Slight oedema or itching are less frequently seen at the site of application. More severe erythema, oedema and/or itching have rarely been reported. This may be due to the local release of histamine and 5-HT.

In very rare instances, blistering of the skin at the site of application may be apparent; in these cases, remove the gel immediately and treat the affected area symptomatically.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

8.5 Post-Market Adverse Reactions

Common: Erythema (slight), Oedema (slight), Pruritus (slight)

Slight erythema is frequently seen at the site of application and is due to the pharmacological action of amethocaine (tetracaine) in dilating capillary vessels. This may help delineating the anaesthetized area.

Slight oedema or itching are less frequently seen at the site of application.

Rare: Erythema (severe)
Oedema (severe)
Pruritus (severe)

Very rare: Blistering. In cases of blistering of the skin at the site of application, remove the gel immediately and treat the affected area symptomatically.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Do not use AMETOP Gel 4% (Tetracaine Hydrochloride Gel) to anaesthetize skin prior to immunization.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory test have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tetracaine is a local anaesthetic and is believed to act by blocking nerve conduction mainly by inhibiting sodium ion influx across the axon membrane. Tetracaine achieves this by acting upon specific receptors that control gating mechanisms responsible for conductance changes in specialised proteinaceous sodium channels.

Blocking sodium ion flux prevents the setting up of an action potential in the nerve axon, thus preventing pain receptors signalling to the central nervous system.

10.2 Pharmacodynamics

Tetracaine additionally has vasodilatory effects, which commonly results in a localised erythema.

10.3 Pharmacokinetics

Absorption:

In vivo (pigs) data has demonstrated that AMETOP Gel 4% (Tetracaine Hydrochloride Gel) is 15 ± 11% bioavailable when administered to intact normal skin, with mean absorption and elimination half lives of 1.23 ± 0.28hours. No un-metabolised tetracaine has been conclusively detected in human plasma following topical administration.

Distribution:

In vitro studies using human plasma show that AMETOP Gel 4% is metabolised rapidly in the blood by plasma pseudocholinesterase, suggesting that AMETOP Gel 4% will have an effect only at the site of application and will have no systemic effects.

Metabolism:

The ester type “caine” anaesthetics are rapidly metabolised in human blood mainly by plasma pseudocholinesterase. In an in vitro study, an initial concentration of tetracaine 3.33 µM (1 µg/ml) in human plasma was found to have been fully metabolised within 20 seconds.

Elimination:

Twelve subjects (6 Females / 6 Males) received topical applications of 10g of AMETOP Gel 4% (400 mg of amethocaine) which was spread over 300 cm^2 on both thighs and covered with a dressing for one hour. No quantifiable amethocaine was found in plasma samples. However, p-(n-butylamino) benzoic acid (BABA), the major metabolite of tetracaine, was found in most samples, and had a mean lag time of 1.5 ± 0.9 hours, tmax of 4.6 ± 2.3 hours and Cmax of 65 ± 50 ng/mL. Low levels of amethocaine, 11 to 78 ng / mL, were found in seven of ten urine samples (4 – 10 hours).

Peak plasma levels of p-(n-butylamino) benzoic acid (BABA), the major metabolite of amethocaine, are between 3-6 hours post dose.

11 STORAGE, STABILITY AND DISPOSAL

Temperature:

Keep refrigerated at 2° to 8°C.

Do not freeze.

Protect from heat.

Others:

Keep in a safe place out of the reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

As tetracaine can cause contact sensitization reactions, particularly with repeated contact, healthcare professionals are advised to wash their hands thoroughly after use, to avoid contamination of other parts of the body. It may be advisable to use a finger cot or protective glove during application and removal of AMETOP Gel 4% (Tetracaine Hydrochloride Gel).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

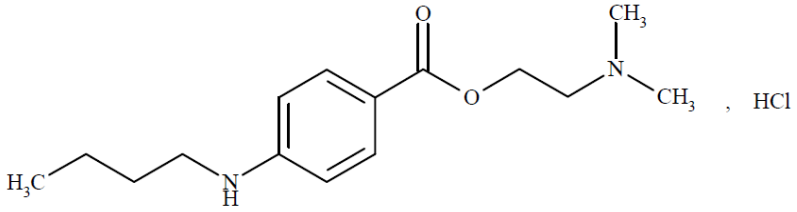
Drug Substance

Proper name: Tetracaine

Chemical name: Tetracaine hydrochloride

Molecular formula and molecular mass: $C_{15}H_{24}N_2O_2$ and 264.37 g/mol

Structural formula:



Physicochemical properties:

Melting point : about 148°C (mixture of Tetracaine polymorphs: 134 - 150°C)

Solubility: Freely soluble in Water and Ethanol 96%

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether AMETOP GEL 4% affects fertility in males or females.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

AMETOP Gel 4%

tetracaine (as tetracaine hydrochloride) gel

Read this carefully before you start taking **AMETOP Gel 4%** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **AMETOP Gel 4%.**

What is AMETOP Gel 4% used for?

AMETOP Gel 4% is used to temporarily numb the skin. This reduces the pain experienced when needles are used to take a blood sample or when an intravenous line is inserted.

How does AMETOP Gel 4% work?

AMETOP Gel 4% is an anaesthetic which is applied to the skin. It blocks nerves in the skin to reduce sensation and cause numbness. This prevents you from feeling pain.

What are the ingredients in AMETOP Gel 4%?

Medicinal ingredients: tetracaine hydrochloride

Non-medicinal ingredients: potassium phosphate, purified water, sodium chloride, sodium hydroxide, sodium methylparaben, sodium propylparaben and xanthan gum

AMETOP Gel 4% comes in the following dosage forms:

Gel; 4% w/w

Do not use AMETOP Gel 4%:

- in premature babies or newborns less than one month of age.
- if you or your child are allergic to tetracaine, any other drug product ending in “caine”, or any of the non-medicinal ingredients in AMETOP Gel 4% (see **What are the ingredients in AMETOP Gel 4%?**).
- on broken skin, large areas of the body, inside your nose or mouth or on your eyes, ears or genitals.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AMETOP Gel 4%. Talk about any health conditions or problems you may have, including if you:

- have epilepsy.
- are pregnant.
- are breastfeeding. It is not known if AMETOP Gel 4% passes into breastmilk.

Other warnings you should know about:

- AMETOP Gel 4% contains sodium methylparaben and sodium propylparaben which may cause allergic reactions. These reactions can happen immediately after AMETOP Gel 4% is applied or can be delayed.
- Do not use more than the recommended dose. Larger amounts of AMETOP Gel 4% must only be applied under the direct supervision of a healthcare professional.
- Children and infants are more likely to experience side effects. Watch your child/infant closely while you are applying AMETOP Gel 4% and after it has been applied.
- Talk to your healthcare professional immediately if the following symptoms appear: weakness, confusion, headache, breathing difficulties and/or change in the colour of the skin.
- Side effects are more likely to occur if you apply large amounts of AMETOP Gel 4% to irritated or broken skin, or if you apply large amounts and cover the treated area with a bandage.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with AMETOP Gel 4%:

- Do not use AMETOP Gel 4% to numb the skin before receiving a vaccine.

How to take AMETOP Gel 4%:

- AMETOP Gel 4% is for external use only.
- Do not apply AMETOP Gel 4% for longer than the recommended times. The numbing effect of AMETOP Gel 4% will last for 4 to 6 hours after a single application.
- Apply AMETOP Gel 4% only to the area of skin to be numbed.
- Apply AMETOP Gel 4% to the skin starting from the centre of the site where the needle is to be inserted. After is has been applied cover the area with a bandage that protects from air and water.
- The contents from one tube (1.5g) is enough to cover and numb an area of skin up to 30 cm^2 (6 x 5 cm). Smaller areas can be numbed in children and infants.
- Wait 30 minutes after applying AMETOP Gel 4% before getting a needle or having blood taken. Wait 45 minutes after applying AMETOP Gel 4% before getting an intravenous line inserted.
- After the above recommended times, remove AMETOP Gel 4% with a gauze swab. The area can now be prepared by your healthcare professional in the normal manner before they insert the needle or intravenous line.
- Wear a rubber glove to apply or remove AMETOP Gel 4%.
- Always wash your hands carefully after using AMETOP Gel 4%.

Usual dose:

<u>Adults (including the elderly):</u>

- Do not apply more than 1 tube per site where a needle or an intravenous line is to be inserted.
- A maximum of 5 sites may be numbed at the same time.
- Do not use more than 7 tubes of AMETOP Gel 4% in a 24-hour period.

Children (over 1 month of age):

- Do not apply more than 1 tube at separate sites in a single application.
- Do not use more than 2 tubes of AMETOP Gel 4% in a 24-hour period.

Overdose:

If you think you, or a person you are caring for, have taken too much **AMETOP Gel 4%**, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using AMETOP Gel 4%?

These are not all the possible side effects you may have when taking AMETOP Gel 4%. If you experience any side effects not listed here, tell your healthcare professional.

Side effects on the skin where AMETOP Gel 4% is applied may include:

- redness
- swelling
- itching
- blistering. If blisters occur, removed AMETOP Gel 4% immediately

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Weakness, confusion, headache, breathing difficulties and/or change in the colour of the skin			✓
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep refrigerated at 2° to 8° C. Do not freeze. Protect from heat.

Keep out of sight and reach of children.

If you want more information about AMETOP Gel 4%:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.valeopharma.com, or by calling 1-855-694-0151.

This leaflet was prepared by Valeo Pharma Inc.

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