PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTOLAK®

Fluorouracil Cream
4% (w/w) fluorouracil (as fluorouracil sodium)

Topical

House Standard

Topical antineoplastic agent
L01BC02

Manufacturer:
Hill Dermaceuticals, Inc.
2650 South Mellonville Ave.
Sanford, Florida
32773 U.S.A.
www.hillderm.com

Canadian Distributor:
Hill Dermaceuticals, Inc.
3045 Southcreek Road, Unit #4
Mississauga, Ontario L4X 2X6
Canada

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January 31, 2019

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RECENT MAJOR LABEL CHANGES

N/A

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Tolak® (fluorouracil cream), 4% (w/w), is indicated for the topical treatment of actinic keratosis lesions of the face, ears, and/or scalp.

1.1 Pediatrics

Actinic keratosis is not usually observed in the pediatric population except in the case of rare genetic diseases. Tolak® is not intended for use in pediatric patients. The safety and efficacy of Tolak® in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. [see WARNINGS AND PRECAUTIONS, *Pediatrics (6.1.3)*]

1.2 Geriatrics

No dose adjustment is required for elderly patients [see CLINICAL TRIALS (13)]. The mean age of the 403 subjects treated with Tolak® in the clinical trials was 68 years. Of the Tolak®-treated subjects, 61% were age 65 and over, while 28% were 75 and over.

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

2 CONTRAINDICATIONS

Tolak® is contraindicated:

- During pregnancy [see WARNINGS AND PRECAUTIONS, *Pregnant Women (6.1.1)*].
- In patients with dihydropyrimidine dehydrogenase (DPD) deficiency [see WARNINGS AND PRECAUTIONS (6)].
- In patients with known hypersensitivity to any of its ingredients.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- Tolak® is for topical use only.
- Not for ophthalmic, oral or intravaginal use.
- Airtight or occlusive dressing should be avoided.
- Tolak® can potentiate skin sensitivity to sunlight and cause severe sunburn.

3.2 Recommended Dose and Dosage Adjustment

Tolak® is applied once daily in an amount sufficient to cover the lesions of the face, ears, and/or scalp with a thin film, gently massaged uniformly into the skin. Tolak® is applied for a period of 4 weeks as tolerated.

Health Canada has not authorized an indication for pediatric use [see WARNINGS AND PRECAUTIONS, *Pediatrics (6.1.3)*].

3.3 Administration

Tolak® is applied once a day to the AK lesions and surrounding areas, for 4 weeks. Tolak® should not be applied around the eyes, in the nose, mouth or mucous membranes; local inflammation and ulceration can occur.
Application of Tolak® is as follows:

- Gently wash, rinse, and pat dry the skin areas to be treated.
- Apply a thin film of the Tolak® to the areas to be treated.
- Gently massage Tolak® evenly into the skin.
- Avoid contact with other areas of the body, and transfer of Tolak® to other people.
- Wash hands well after application of Tolak®.

3.4 Missed Dose

If a dose of this medication is missed, it is not necessary to make up the missed dose. Skip the missed dose and continue with the next scheduled dose.

4 OVERDOSAGE

There are no known reports of overdose with topical 5-FU. A literature report describes total body application of 5-FU to 2 patients with extensive non-melanoma skin cancers; while pain and secondary infections were important side effects, the authors say that the treatment was used successfully in these 2 patients.

In case of accidental ingestion, contact the hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	Cream / 4%(w/w) fluorouracil (as fluorouracil sodium)	arlacel-165, butylated hydroxytoluene, cetyl alcohol, anhydrous citric acid, glycerin, isopropyl myristate, methyl gluceth-10, methylparaben, propylparaben, purified water, peanut oil, sodium hydroxide, stearic acid, and stearyl alcohol.

Tolak is supplied in a 40 g aluminum tube.

6 WARNINGS AND PRECAUTIONS

Application Site Adverse Reactions

Application site reactions (erythema, scaling/dryness, edema, crusting, erosions, stinging/burning, and pruritus) were observed in almost all patients during treatment of actinic keratosis on the face, ears, and/or scalp with topical fluorouracil [see ADVERSE REACTIONS, *Clinical Trial Adverse Reactions (7.2)*]. In the clinical trials of Tolak®, application site irritation resolved within 4 weeks after discontinuing treatment.

Tolak® should not be applied directly into eyes, nose, mouth, or other mucous membranes because irritation, local inflammation and ulceration can occur.

Embryofetal Toxicity

Cases of miscarriage and birth defects (including cleft lip and cleft palate) have been reported when pregnant women were exposed to a topical or parenteral fluorouracil product. In addition, ventricular septal defect and cases of miscarriage occurred when pregnant women applied a topical fluorouracil product to mucous membranes (Tolak® is not indicated for use on the mucous membrane). Studies in animals have demonstrated that parenteral fluorouracil caused teratogenic and lethal embryo-fetal effects at sub-therapeutic doses. Therefore, Tolak® is contraindicated in pregnancy [see CONTRAINDICATIONS (2)].

Females of childbearing potential must use effective contraception during therapy. A pregnancy test should be performed on all women of childbearing potential prior to Tolak® use [see WARNINGS AND PRECAUTIONS, *Special Populations (6.1), Females of Childbearing Potential (6.1.5)*].

Hypersensitivity Reactions

Allergic contact dermatitis (delayed type hypersensitivity reaction) has been noted for topical fluorouracil drugs. While application site reactions are observed in almost all patients during treatment of actinic keratosis with topical fluorouracil [see ADVERSE REACTIONS, *Post-Market Adverse Reactions (7.3)*], delayed type hypersensitivity should be suspected in the event of severe pruritus or eczema at the application site or at a distant site.

If signs of hypersensitivity occur, patients should discontinue Tolak® immediately and contact their healthcare provider.

Tolak® contains peanut oil. The peanut oil used in Tolak® is tested for residual protein through amino acid analysis; the acceptance criterion for total protein is no more than 0.5 parts per million. Physicians should use caution in prescribing Tolak® for peanut-sensitive individuals [see CONTRAINDICATIONS (2)].

Ophthalmic Adverse Reactions

Corneal and conjunctival disorders have occurred with topical fluorouracil use [see ADVERSE REACTIONS, *Post-Market Adverse Reactions (7.3)*]. Avoid application to the periocular area. To avoid transfer of the drug into the eyes and to the periocular area during and after application, patients should wash hands well after applying Tolak®. If accidental exposure occurs, the patient should flush eye(s) with large amounts of water and seek medical care as soon as possible.

Photosensitivity

Topical fluorouracil is associated with photosensitivity reactions including severe sunburn.

Minimize exposure to ultraviolet rays including sunlight, sun lamps, and tanning beds during and immediately following treatment with Tolak® because the intensity of the photosensitivity reaction may be increased.

Toxicity in Patients with Dihydropyrimidine Dehydrogenase Deficiency
Tolak® must not be used on patients with dihydropyrimidine dehydrogenase (DPD) deficiency [see CONTRAINDICATIONS (2)]. Life-threatening systemic toxicity has been reported with the topical use of fluorouracil in a patient with DPD deficiency. Symptoms of serious side effects included severe stomach-area abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, and inflammation of the esophagus, stomach and small bowel.

A large percentage of fluorouracil is catabolized by the DPD enzyme. DPD enzyme deficiency may result in increased availability of fluorouracil to the anabolic pathway, which may lead to increased interference with DNA and RNA synthesis and increased cytotoxic activity and potential toxicities [see ACTION AND CLINICAL PHARMACOLOGY, *Pharmacokinetics (9.2)*]. Therefore, Tolak® is contraindicated in patients with DPD deficiency.

Patients should discontinue Tolak® if symptoms of fluorouracil's systemic toxicity develop.

6.1 Special Populations

6.1.1 Pregnant Women

There is no clinical data regarding the use of Tolak® in pregnant women. Because fluorouracil is a known human teratogen (Teratogenic Effects: Pregnancy Category X), Tolak® must not be used during pregnancy [see CONTRAINDICATIONS (2)].
Cases of miscarriage and birth defects (including cleft lip and cleft palate) have been reported when pregnant women were exposed to a topical or parenteral fluorouracil product. In addition, ventricular septal defect and cases of miscarriage occurred when pregnant women applied a topical fluorouracil product to mucous membranes (Tolak® is not indicated for use on the mucous membrane).

Animal reproduction studies have shown that parenterally administered fluorouracil caused embryofetal toxicity at doses lower than the usual human intravenous dose [see WARNINGS AND PRECAUTIONS (6), Embryofetal toxicity and NON-CLINICAL TOXICOLOGY (14).

6.1.2 Breast-feeding

Tolak® should not be used when breastfeeding or plan to breastfeed.
It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk and there is some systemic absorption of fluorouracil after topical administration, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue drug use, taking into account the importance of the drug to the mother.

6.1.3 Pediatrics

Actinic keratosis is not usually observed in the pediatric population except in the case of rare genetic diseases. Tolak® is not intended for use in pediatric patients. Safety and effectiveness in pediatric patients has not been established; therefore, Health Canada has not authorized an

indication for pediatric use.

6.1.4 Geriatrics

No dose adjustment is required for elderly patients [see CLINICAL TRIALS (13)]. The mean age of the 403 subjects treated with Tolak® in the clinical trials was 68 years. Of the Tolak®-treated subjects, 61% were 65 and over, while 28% were 75 and over.

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

6.1.5 Females of Childbearing Potential (FCBP)

A FCBP is defined as a female who meets at least **one** of the following criteria:
- is menstruating,
- is amenorrhoeic and has not entered menopause (menopause should be clinically confirmed),
- is perimenopausal

A pregnancy test should be performed on all women of childbearing potential prior to Tolak® use. Females who are able to become pregnant should use an effective method of birth control during treatment with Tolak® and for one month after the last dose of Tolak®.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The following adverse reactions are discussed in more detail under WARNINGS AND PRECAUTIONS (6):
- Application Site Adverse Reactions
- Embryofetal toxicity
- Hypersensitivity Reactions
- Ophthalmic Adverse Reactions
- Photosensitivity
- Toxicity in Patients with Dihydropyrimidine Dehydrogenase Deficiency [also see CONTRAINDICATIONS *(2)*].

7.2 Clinical Trial Adverse Reactions

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

The data described below reflect exposure to Tolak® in 397 subjects with actinic keratosis in vehicle-controlled Phase III clinical studies (Trials 1 and 2). The population ranged in age from 33 to 94 years, was 80% male, and almost all were Caucasian. Most subjects were treated with Tolak® once daily for 4 weeks. In Trials 1 and 2, 12% of Tolak®-treated and 4% of vehicle-treated subjects discontinued treatment because of adverse reactions. Of these subjects, the majority had adverse reactions at the application site. Ophthalmic adverse reactions (eye

irritation and periorbital edema), leading to discontinuation, occurred in one subject for periorbital edema and two subjects for eye irritation with Tolak® use.

The most common adverse reactions reported in clinical trials with Tolak® throughout the 4-week treatment and the 4-week post-treatment periods, wereadverse reactions related to tolerability, including erythema, scaling/dryness, edema, crusting, erosions, stinging/burning, and pruritus. These adverse reactions are likely to be related to the pharmacologic action of 5-fluorouracil in the clearing of actinic keratosis lesions. The severity of the local adverse reactions in subjects using Tolak® generally increased over the 4-week treatment period, usually reaching maximal scores at 4 weeks of treatment and resolving within 4 weeks after cessation of treatment.

The number and percentage of subjects with each of application site reactions at one or more post-baseline visit(s) during the clinical trials are shown in Table 1.

Table 1: Number and Percentage of Subjects with Application Site Adverse Reactions with Tolak® Treatment in Clinical Trials 1 and 2

	Tolak® N=397 n (%)		Vehicle N=120 n (%)	
Adverse event/Severity	**Mild, Moderate or Severe**	**Severe Only**	**Mild, Moderate or Severe**	**Severe Only**
Erythema	394 (99%)	174 (44%)	102 (85%)	0 (0%)
Scaling/ Dryness	377 (95%)	94 (24%)	99 (83%)	0 (0%)
Crusting	346 (87%)	87 (22%)	46 (38%)	0 (0%)
Pruritus	337 (85%)	65 (16%)	46 (38%)	1 (1%)
Stinging/ Burning	346 (87%)	101 (25%)	42 (35%)	0 (0%)
Edema	275 (69%)	30 (8%)	11 (9%)	0 (0%)
Erosions	271 (68%)	44 (11%)	14 (12%)	0 (0%)

Treatment-related AEs reported by at least 1% of the subjects in the Tolak® treated groups were application site reactions which included irritation, pain, errosion and inflammation; other treatment-related AEs reported were eye disorders (eye irritation and eye swelling), and insomnia.

Based on safety data from Trial 1, a randomized, double-blind well controlled trial in subjects with actinic keratosis, the safety profile for Tolak® was similar to that of its active comparator Efudex. Overall incidence of adverse events was comparable between the Tolak® (n=348) and Efudex (n=342) safety populations (34% and 36%, respectively). The frequency of these adverse events excludes the tolerability assessments of erythema, scaling/dryness, crusting, pruritus, stinging/burning, edema, and erosions. Adverse events classified to MedDRA (Version 9.0) system organ class (SOC) of General disorders and administration site conditions were reported in 16% and 21% of subjects and adverse events of Infections and infestations SOC were reported in 6% and 7% of subjects in the Tolak® and Efudex groups, respectively. All other adverse events specific as well as by SOC were reported in ≤ 2% of subjects treated with

Tolak®. These results are consistent with the low systemic absorption of fluorouracil after dermal administration of Tolak® [see ACTION AND CLINICAL PHARMACOLOGY, *Pharmacokinetics (9.2)*].

7.3 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of topical fluorouracil. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: leukocytosis, pancytopenia, thrombocytopenia, eosinophilia, neutrophil toxic granulation
Eye disorders: corneal disorder, conjunctival disorder, eye irritation, conjunctivitis, lacrimation
Gastrointestinal disorders: stomatitis
General Disorders and Administration Site Conditions: medicinal taste
Infections and Infestations: herpes simplex
Neoplasms*:* chronic lymphocytic leukemia, non-melanoma skin cancer
Nervous system disorders: insomnia, irritability
Psychiatric disorders: emotional distress
Skin and subcutaneous tissue disorders: blistering, allergic contact dermatitis, photosensitivity, pain, scarring, skin irritation, rash, ulceration, hyperpigmentation, alopecia, bullous pemphigoid, ichthyosis, suppuration, swelling, soreness, telangiectasia, tenderness, urticaria

8 DRUG INTERACTIONS

8.1 Overview

Subjects using systemic steroids, immunosuppressants, and immunomodulators were generally excluded from the clinical studies of Tolak®, as were subjects who used retinoids, topical steroids, glycolic acid products, alpha-hydroxy products, and chemical peeling products in the treatment areas. No clinical trials were designed to specifically evaluate drug interactions.

8.2 Drug-Drug Interactions

Systemic concentrations of fluorouracil after topical dermal administration of Tolak® appear to be low and as such are considered unlikely under normal circumstances to significantly influence the pharmacokinetics of other concomitantly administered systemic drugs (see ACTION AND CLINICAL PHARMACOLOGY, *Pharmacokinetics (9.2)*). Because life-threatening systemic toxicity has been reported with the topical use of fluorouracil in a patient with DPD deficiency (see WARNINGS AND PRECAUTIONS (6)), concomitant use of substances that decrease the activity of DPD (such as capecitabine, brivudine, sorivudine, and interferon-α) could result in a pronounced increase in systemic fluorouracil concentrations and associated toxicity and is therefore not advised (see WARNINGS AND PRECAUTIONS (6) and ACTION AND CLINICAL PHARMACOLOGY, *Pharmacokinetics (9.2)*).

Systemic administration of fluorouracil or its prodrugs has led to signs of increased activity and adverse effects of CYP2C9 substrates such as warfarin and phenytoin. Bleeding complications have been observed upon concomitant administration with warfarin, and symptoms of phenytoin intoxication have been observed upon concomitant administration with phenytoin. The

possibility of drug interactions between Tolak® and CYP2C9 substrates, particularly those with a narrow therapeutic index, should be considered.

Systemic interactions between Tolak® and other concomitantly administered systemic drugs may be more pronounced in patients with DPD deficiency. When DPD deficiency is suspected, the possibility of drug interactions between systemically absorbed fluorouracil and the concomitant medicines should be considered. The possibility of DPD deficiency when drug interactions are suspected should also be considered.

Concomitant administration of leucovorin may enhance both the activity and toxicity of fluorouracil by increasing the inhibition by fluorouracil of the enzyme thymidylate synthase. The relevance of this activity to the topical dermal use of Tolak® in the treatment of actinic keratosis lesions is likely to be minimal due to the low systemic absorption of fluorouracil after topical dermal administration as Tolak®.

8.3 Drug-Food Interactions

Interactions with foods have not been studied.

8.4 Drug-Herb Interactions

Interactions with herbal products have not been studied.

8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

8.6 Drug-Lifestyle Interactions

Interactions with various lifestyles have not been studied.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Fluorouracil acts by at least 3 known mechanisms. First is by inhibition by fluorodeoxyuridine monophosphate of the enzyme thymidylate synthase, which catalyzes the conversion of uridylate to thymidylate. This action inhibits DNA synthesis by blocking formation of the nucleic acid thymidine which is essential for DNA synthesis. Second is by the erroneous incorporation of fluoro-deoxyuridine triphosphate into DNA, resulting in DNA damage. Third is by the erroneous incorporation of fluorouridine triphosphate into RNA, leading to disruptions in RNA function. The effects of DNA and RNA deprivation are most marked on those cells that grow more rapidly and take up fluorouracil at a more rapid rate. An additional mechanism of action may be the activity of fluorouracil against viruses that may be associated with the development of actinic keratosis.

9.2 Pharmacokinetics

Absorption: Absorption of fluorouracil both into and through the skin depends on the concentration and formulation of fluorouracil, as well as application to healthy versus diseased

skin. In general, systemic absorption after topical dermal application appears to be low, including after topical dermal application of Tolak®.

A systemic absorption study of topically applied Tolak® was performed in 21 patients with at least 3 actinic keratosis lesions (4 mm or greater in diameter). The concentration of 5-fluorouracil in plasma was examined at 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours after the last dose of a 4-week regimen in subjects with actinic keratosis after "area application" to area(s) in which actinic keratosis lesions were identified at baseline. Areas were defined as the whole region of the left cheek, right cheek, chin and forehead, bald scalp, and right and left ears, where actinic keratosis was identified at baseline. Thus, for example, if an actinic keratosis lesion was identified on the left cheek, Tolak® was to be applied as a thin film to the whole area of the left cheek.

Eight patients had undetectable levels of plasma 5-fluorouracil (the lower limit of quantification was 1.00 ng/ml) in all plasma samples following treatment with Tolak®. Among patients with detectable plasma 5-fluorouracil levels, the highest level of plasma 5-fluorouracil was generally observed at 1 hour post-dose. The mean observed maximum concentration (± standard deviation) of plasma 5-fluorouracil was 3.66 (±1.58) ng/mL with the range between 1.11 – 7.35 ng/mL.

Distribution: When present systemically, fluorouracil is distributed to all body tissues including the brain. Distribution after topical dermal administration of Tolak® to tissues other than the skin is expected to be low due to minimal systemic absorption.

Metabolism: Fluorouracil is metabolized into 3 active metabolite including fluorodeoxyuridine monophosphate, which inhibits the enzyme thymidylate synthase; fluoro-deoxyuridine triphosphate, which can be incorporated into DNA; and fluorouridine triphosphate, which can be incorporated into RNA (see ACTION AND CLINICAL PHARMACOLOGY, *Mechanism of Action (9.1)*). Fluorouracil is also catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD); catabolism by this pathway results in inactive degradation products (such as CO2, urea, α-fluoro-β-alanine). In the absence of the DPD, formation of these metabolites is prevented leading to increased levels and life-threatening systemic toxicity of fluorouracil (see CONTRAINDICATIONS (2), WARNINGS AND PRECAUTIONS (6), Toxicity in Patients with Dihydropyrimidine Dehydrogenase Deficiency).

Elimination: The percentage of fluorouracil that is eliminated systemically after topical dermal administration of Tolak® is unknown. Systemic fluorouracil is eliminated mainly in the urine as its degradation products (urea and α-fluoro-ß-alanine) and to a lesser extent as unchanged drug. No data are available regarding the elimination of fluorouracil and metabolites that either remain on the skin or are absorbed into the skin but do not enter the systemic circulation.

10 STORAGE, STABILITY AND DISPOSAL

Store Tolak® at 20°C - 25°C. Do not freeze.

Tolak® has a full shelf life of 24 months under the required storage conditions.

Medicines should not be disposed of down the drain or in household garbage.

11 SPECIAL HANDLING INSTRUCTIONS

- Do not freeze Tolak®.
- Do not use Tolak® after the expiration date printed on the tube.

Keep Tolak® and all medicines out of the reach of children.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

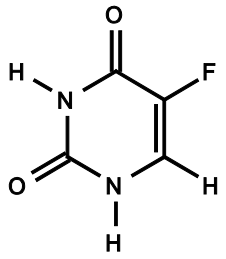
Drug Substance

Proper name: Fluorouracil

Chemical name: 5-fluoro-2,4 (1H,3H)-pyrimidinedione

Molecular formula and molecular mass: $C_4H_3FN_2O_2$, and 130.1.

Structural formula:



Physicochemical properties:

(a) Physical description (e.g., appearance, colour, physical state):
White to almost white, crystalline powder

(b) Physical form (e.g., polymorphic form, solvate, hydrate):
No potential polymorphism

(c) Solubilities (e.g., in common solvents, aqueous/nonaqueous solubility profile): Sparingly soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in chloroform and ether.

(d) pH and pKa values:
pKa1: 8.0 ± 0.1
pKa2: 13.0 ± 0.1
pH: 4.5 to 5 (0.5 g / 50 ml H_2O)

(e) Other (e.g., partition coefficients, melting or boiling points, optical rotation, refractive index (for a liquid), hygroscopicity, UV absorption maxima and molar absorptivity):
Melting point: 280 to 284 °C
Chirality: No potential isomerism; no optical activity
Hygroscopicity: Non hygroscopic

13 CLINICAL TRIALS

The efficacy and safety of Tolak® was evaluated in two well-controlled double-blind multi-center trials (Trial 1 and Trial 2). Trial 1 was designed to evaluate the safety and efficacy of once daily application over four weeks of Tolak® 4%(w/w), compared with four week applications of: 1) twice daily application of Efudex® 5% cream; 2) once daily with the Tolak® vehicle cream; and 3) comparator vehicle cream applied twice daily. Trial 2 was designed to evaluate the safety and efficacy of once daily application of Tolak® 4%(w/w) compared with Tolak® vehicle cream. In both studies, subjects were included who had at least 5 previously untreated AK lesions on the face and/or ears and/or scalp, which were at least 4 mm in longest diameter, were clinically typical nonhypertrophic and/or nonhyperkeratotic, and none of the AK lesions exceeded 1 cm in size. Subjects were excluded if AK lesions were in areas that were hyperkeratotic or contained lesions which were clinically suspected to be squamous cell carcinoma. AK lesions were evaluated at Baseline and again at Week 1 (during treatment), Week 2 (during treatment), Week 4 (end of treatment), Week 6 (2 weeks off treatment), and Week 8 (4 weeks off treatment). Adverse event (AE) information and tolerability (severity of erythema, scaling/dryness, crusting, pruritus, stinging/burning, edema, and erosions) were also evaluated at these same time intervals.

Subjects applied the assigned medication (Tolak® or vehicle placebo) to the face, and/or ears and/or scalp once daily for four weeks as directed. Application of the medication involved field treatment of the whole area of the face and/or ears and/or scalp where actinic keratosis lesions were identified at baseline. Subjects receiving confounding treatments or medications were excluded. The effect of treatment was assessed at 4 weeks post-treatment. Subjects were almost all Caucasian, the mean age was approximately 68 years (range was from 33 to 89 years), and the mean number of actinic keratosis lesions was 14.4 in the Tolak® group and 16.2 in the vehicle group in Trial 1, and 19.2 in the Tolak® group and 23.2 in the vehicle group in Trial 2.

Summary of patient demographics, disease characteristics of study population, and Disposition of Subjects (Trial 1 and Trial 2 Combined) are provided in Tables 2, 3 and 4, respectively.

Table 2: Demographic Characteristics: Safety Population (Trial 1 and 2 combined)

Characteristic	4%(w/w) TRADENAME Cream (N=397)	TRADENAME Vehicle Cream (N=120)
Age, years		
Mean	67.7	67.6
Median	68.0	69.6
SD	10.0	10.8
Range	36.7-88.9	33.5-87.8
Gender, n (%)		
Male	322 (81)	104 (87)
Female	75 (19)	16 (13)
Ethnicity, n (%)		
Hispanic/Latino	15 (4)	1 (1)
Not Hispanic/Latino	382 (96)	119 (99)
Race, n (%)		
White	392 (99)	120 (100)
Black/African American	0	0
Asian	0	0
American Indian/Alaska Native	1 (<1)	0
Native Hawaiian/Pacific Islander	0	0
Other	4 (1)	0
Skin Type, n (%)		
I	88 (22)	19 (16)
II	194 (49)	60 (50)
III	99 (25)	36 (30)
IV	13 (3)	4 (3)
V	3 (1)	1 (1)
VI	0	0

Table 3: Analysis of Disease Baseline Characteristics: Safety Population (Trial 1 and 2 combined)

	Tolak® % (n/N)	Vehicle % (n/N)
	(N=397)	**(N=120)**
Total number of Lesions		
Mean	15.1	19.1
Median	11.0	14.0
STD	11.6	16.9
Range	5.0 – 83.0	5.0 – 90.0
Baseline Severity		
Mild (5-10 lesions)	181 (46%)	43 (36%)
Moderate (11-25 lesions)	162 (41%)	55 (46%)
Severe (> 25 lesions)	54 (14%)	22 (18%)

Table 4: Disposition of Subjects (Trial 1 and Trial 2 Combined)

	Tolak®	**Vehicle**
Combined Total		
Number of Subjects Enrolled	**403**	**120**
Number of Subjects Excluded from Intent-to-Treat Analyses	0	0
Number of Subjects Included in Intent-to-Treat Analyses	403	120
Number of Subjects Excluded from Safety Analyses	6	0
Number of Subjects Included in Safety Analyses	397	120
	Tolak® (N=403)	**Vehicle (N=120)**
Number of Subjects Who Completed the Treatment Phase of the Study	341	116
Reasons for Discontinuation from Treatment Phase		
Treatment Failure	0	0
Adverse Event	46	4
Subject's Decision to Withdraw	11	0
Non-Compliance	1	0
Lost to Follow-Up	1	0
Pregnancy	0	0
Other	2	0
Not Reported	1	0
Number of Subjects Who Completed the Study	386	113
Reasons for Study Discontinuation		
Treatment Failure	0	0
Adverse Event	2	3
Subject's Decision to Withdraw	10	2
Non-Compliance	1	0
Lost to Follow-Up	3	0
Pregnancy	0	0
Other	1	2

The number and percentage of subjects with 100% clearing of their actinic keratosis lesions and with at least 75% clearing of their actinic keratosis lesions are shown in Table 5.

Table 5: Subjects with 100% and at least 75% Clearing of Actinic Keratosis Lesions at 4 Weeks Post-Treatment

	Tolak® % (n/N)	Vehicle % (n/N)	p-Value
Subjects with 100% Clearing of Actinic Keratosis Lesions			
Trial 1	54% (192/353)	4% (3/70)	<0.001
Trial 2	24% (12/50)	4% (2/50)	0.004
Subjects with At Least 75% Clearing of Actinic Keratosis Lesions			
Trial 1	80% (284/353)	7% (5/70)	<0.001
Trial 2	74% (37/50)	10% (5/50)	<0.001

Examination of age (< 68 years versus ≥ 68 years) and gender subgroups did not identify differences in response to Tolak® among these subgroups. There were too few non-Caucasian subjects to adequately assess differences in effects among racial subgroups.

14 NON-CLINICAL TOXICOLOGY

14.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate long-term studies in animals to evaluate carcinogenic potential of fluorouracil have not been conducted. Studies with the active ingredient of Tolak®, fluorouracil, have shown mutagenic effects in in vitro and in vivo tests and impairment of fertility in in vivo animal studies.

Fluorouracil was positive in three in vitro cell neoplastic transformation assays. In the C3H/10T½ clone 8 mouse embryo cell system, the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed syngeneic mice.

Although no evidence for mutagenic activity of fluorouracil was observed in 3 studies utilizing the Ames test, mutagenic activity was observed in the survival count rec-assay with Bacillus subtilis and in the Drosophila wing-hair spot test. Fluorouracil produced petite mutations in Saccharomyces cerevisiae and demonstrated positive results in the micronucleus test using bone marrow cells of male mice.

Fluorouracil demonstrated clastogenic activity in vitro in Chinese hamster fibroblasts at concentrations of 1.0 and 2.0 µg/mL and was associated with chromatid gaps, breaks, and exchanges. In human lymphocytes, fluorouracil increased sister chromatid exchange in vitro. Additionally, an increase in numerical and structural chromosome aberrations have been observed in peripheral lymphocytes of patients treated with 5-fluorouracil.

Fluorouracil administered parenterally has been shown to be teratogenic in mice, rats, and hamsters when given at doses below the usual human intravenous dose of 12 mg/kg. Fluorouracil exhibited maximum teratogenicity when given to mice as single intraperitoneal injections of 10 to 40 mg/kg (human equivalent dose, HED= 0.8 to 3.2 mg/kg) on day 10 or 12 of gestation. A single intraperitoneal dose of 40 mg/kg fluorouracil on day 10 of gestation produced 96 % embryolethality and 100% surviving fetal malformations. Similarly, intraperitoneal doses of 12 to 37 mg/kg (HED= 1.9 to 6.0 mg/kg) given to rats between days 9 and 12 of gestation and intramuscular doses of 3 to 9 mg/kg (HED=5-15 mg/kg) given to hamsters between days 8 and 11 of gestation were teratogenic and/or embryotoxic. The rate of

malformations observed in hamster fetuses when the mother received a single intramuscular injection was related to the dose and time of drug administration. A single dose of 30 mg/kg (HED =4.8 mg/kg) injected to pregnant rats produced 88% lethality, and 100% malformed survivors. In monkeys, divided doses above 40 mg/kg (HED=12.96 mg/kg) given between days 20 and 24 of gestation resulted in spontaneous abortions.

In rats, chromosomal abnormalities and changes in chromosome organization in spermatogonia have been observed after intraperitoneal administration of 125 to 250 mg/kg of fluorouracil. Spermatogonial differentiation was also inhibited and resulted in transient infertility. Fluorouracil was inactive, however, at oral doses of 5 to 80 mg/kg/day in studies with a strain of mouse which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens. In female rats, fluorouracil administered intraperitoneally at doses of 25 and 50 mg/kg during the preovulatory phase of oogenesis resulted in a significant reduction in the incidence of fertile matings, a delay in the development of preimplantation and postimplantation embryos, an increased incidence of preimplantation lethality, and an induction of chromosomal anomalies in these embryos. In mice, single intravenous or intraperitoneal injections of fluorouracil were toxic to differentiated spermatogonia and spermatocytes (at 500 mg/kg) and produced abnormalities in spermatids (at 50 mg/kg).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrTolak®
Fluorouracil Cream
4%(w/w) fluorouracil (as fluorouracil sodium)

Read this carefully before you start using Tolak® 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 Tolak®.

What is Tolak® used for?

Tolak® is used in adults to treat actinic keratosis (AK) on the face, ears, or scalp. AK is a rough, crusty or scaly patch on the top layer of skin that is made up of fast growing pre-cancerous cells.

It is not known if Tolak is safe and effective in children.

How does Tolak® work?

Tolak® works by destroying the AK cells. The active ingredient in Tolak®, fluorouracil, enters the AK cells. This interrupts the function of the cell causing it to die.

As Tolak® destroys abnormal AK cells, the skin becomes irritated. The skin will return to normal within 4 weeks after stopping treatment.

What are the ingredients in Tolak®?

Medicinal ingredients: fluorouracil (as fluorouracil sodium)
Non-medicinal ingredients: arlacel-165, butylated hydroxytoluene, cetyl alcohol, anhydrous citric acid, glycerin, isopropyl myristate, methyl gluceth-10, methylparaben, peanut oil, propylparaben, purified water, sodium hydroxide, stearic acid, and stearyl alcohol.

Tolak® comes in the following dosage forms:

Cream, 4% (w/w)

Do not use Tolak® if:

- You are pregnant or may become pregnant.
  Females who are pregnant or plan to get pregnant:
  - Tolak® may harm your unborn child or may make you lose the pregnancy.
  - Before you start using Tolak®, a pregnancy test should be performed on all women who can get pregnant.
  - You should use effective methods of birth control while taking Tolak®. Keep using birth control for 1 month after the last time you use Tolak®.
  - Talk to your healthcare professional about methods of birth control that may be right for you during your treatment with Tolak®.
  - If you do become pregnant while taking Tolak®, stop using it and tell your healthcare professional right away.
- Your body does not make enough of (you are deficient in) the enzyme called dihydropyrimidine dehydrogenase (DPD). If you do not have enough of this enzyme, you

may get serious side effects if you use Tolak®. If you have stomach-area abdominal pain, bloody diarrhea, vomiting, fever, and chills, contact your healthcare professional right away. These may be signs that you are experiencing serious side effect of Tolak® use called **systemic toxicity**.
- You are allergic to fluorouracil or any of other ingredients in this medicine. **Tolak® contains peanut oil**.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you use Tolak®. Talk about any health conditions or problems you may have, including if you:
- Are breastfeeding or plan to breastfeed. It is not known if Tolak® passes into breast milk. You and your healthcare professional should decide if you will use Tolak® or breastfeed.
- Are going to be exposed to sunlight, sun lamps, and tanning beds. Exposure to ultraviolet light immediately following application of Tolak® may cause severe sunburn.

Other warnings you should know about:
Avoid applying Tolak® in your eyes, mouth, lips, nostrils or other mucous membranes like the vagina. Irritation, inflammation and ulcers can occur in these areas after applying Tolak®.

Severe skin reactions may occur when using Tolak®. If you experience severe itching or eczema at the spot where you have applied Tolak® or somewhere else on your body, stop using Tolak®. Contact your healthcare professional right away.

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 Tolak®:
- Medicines that affect how well the enzyme DPD works, like capecitabine, brivudine, sorivudine and interferon-α.
- A medicine~~s~~ called warfarin, which is used to prevent blood clots. You may experience bleeding complications if Tolak® is used with warfarin.
- A medicine called phenytoin, which is used to treat seizures.
- A medicine called leucovorin, which may be used in the treatment of some cancers. Leucovorin can increase the action and the side effects of Tolak®.

How to use Tolak®:
Always use Tolak® exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, nurse or pharmacist if you are not sure.
- Before applying Tolak®, gently wash, rinse and pat dry the skin areas to be treated.
- Apply a thin layer of Tolak® to affected areas.
- Gently massage evenly into your skin.
- Use only on affected areas and not on skin that does not have actinic keratosis. Avoid transfer of Tolak® from your body to other people.
- After applying Tolak®, wash your hands well.
- Tolak® is for topical use only. Avoid use in your eyes, mouth, lips, nostrils or vagina.
- **Do not cover the treated areas with an airtight dressing after applying Tolak®.**
- **Avoid sunlight.** Tolak® can make your skin sensitive to the sun. You could get severe sunburn. Limit your time in the sun during treatment with Tolak®.

Usual dose:
Apply Tolak® to affected areas of skin once a day for 4 weeks.

Overdose:

In case of accidental ingestion, contact your health care professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If an application (dose) of this medication is missed, it is not necessary to make up the missed dose. Skip the missed dose and continue with the next scheduled dose.

What are possible side effects from using Tolak®?

These are not all the possible side effects you may feel when using Tolak®. If you experience any side effects not listed here, contact your healthcare professional.

- Reactions at the application site (redness, scaling/dryness, swelling, crusting, breakdown of skin, stinging/burning, and itching).
- Allergic contact dermatitis (severe itching or red rash at treated areas or other areas away from the treatment site).
- Eye irritation
- Eye swelling
- Trouble sleeping

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	
RARE			
Systemic toxicity (symptoms reported with the topical use of fluorouracil in a patient with DPD deficiency): Fever, chills, vomiting, bloody diarrhea, severe abdominal pain.		√	√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to 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 (http://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.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:
Store Tolak® at 20°C to 25°C.
- Do not freeze Tolak®.
- Do not use Tolak® after the expiration date printed on the tube.

Keep out of reach and sight of children.

Medicines should not be disposed of down the drain or in household garbage. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

If you want more information about Tolak®:
- 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 (http://www.canada.ca/en/health-canada.html); the manufacturer's website www.hillderm.com, or by calling 1-800-344-5707.

This leaflet was prepared by Hill Dermaceuticals, Inc.

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