SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tolak 40 mg/g cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of cream contains 40.0 mg of fluorouracil (5-FU).

Excipients with known effect:

Butylhydroxytoluene (E 321) (2.0 mg/ g),
cetyl alcohol (20.0 mg/ g),
methyl parahydroxybenzoate (E 218) (1.8 mg/ g),
propyl parahydroxybenzoate (0.2 mg/ g),
arachis oil, refined (peanut oil) (100.0 mg/ g),
stearyl alcohol (20.0 mg/ g)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream
White to off white cream with alkaline pH at 8.3 to 9.2

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tolak is indicated for the topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade I and II) of the face, ears, and/or scalp in adults.

4.2 Posology and method of administration

Posology

Tolak should be applied once daily in an amount sufficient to cover the whole area of involved actinic skin of the face and/or ears and/or scalp where AK lesions have been identified with a thin film, using the fingertips to gently massage the medication uniformly into the skin.

When assessing options to treat recurrent lesions, the physician should consider that repeated treatment with Tolak in case of recurrence has not been formally assessed. The duration between initial treatment and retreatment with Tolak in clinical studies ranged between 7 and 13 months (mean: 9.4 months). Number of retreatments with Tolak is at the decision of the treating physician.

Duration of treatment

Apply Tolak for a period of 4 weeks as tolerated.

The development of an inflammatory response is associated with the pharmacological action of 5-FU on dysplastic AK cells. The clinical manifestation of response is characterised by local skin reactions including erythema, scaling, crusting, pruritus, burning, oedema and erosions (see section 4.8). These local reactions are essentially mild to moderate with a peak at 4 weeks of treatment. They are transient and resolve within 2-4 weeks after the end of treatment (see also normal pattern of response in section 4.4).

In case of severe discomfort during treatment or for skin reactions lasting more than 4 weeks, symptomatic treatment (such as emollient or topical corticosteroids) should be offered.

Evaluation of the therapeutic effect can be assessed approximately 4 weeks after the end of the treatment.

Method of administration

Prior to application of Tolak, wash, rinse, and dry the treatment areas.

Thoroughly wash hands following Tolak cream application (see section 4.4)

Special populations

Pediatric population

There is no relevant use of Tolak in the pediatric population. No data are available in the pediatric population since children do not have actinic keratosis.

Elderly population

No dedicated studies in elderly patients have been conducted. No dose adjustment is required for elderly patients (65 years and older) based on the results of the clinical studies (see section 5.1).

Hepatic and renal impairment:

No dosage adjustment is required for patients with hepatic or renal impairment

4.3 Contraindications

Tolak is contraindicated:

- In patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- In patients with allergy to peanut or soya (see section 6.1)
- During pregnancy (see section 4.6)
- During breastfeeding (see section 4.6)
- In coadministration with brivudine, sorivudine and analogues as they may lead to a substantial increase in plasma levels of 5-FU and associated toxicity. The antiviral nucleoside drugs brivudine and sorivudine are potent inhibitors of dihydropyrimidine dehydrogenase (DPD), a 5-FU metabolising enzyme (see section 4.4 and 4.5).

4.4 Special warnings and precautions for use

Do not apply Tolak directly into eyes, nose, mouth, or other mucous membranes because irritation, local inflammation and ulceration can occur. Should such contact occur, the cream is to be washed off with plenty of water.

Tolak should not be applied to open wounds or damaged skin where the skin barrier is compromised.

The normal pattern of response includes: an early inflammatory phase (typically characterised by erythema, which may become intense and blotchy), an apoptotic phase (characterised by skin erosion) and finally healing (when epithelialisation occurs). The clinical manifestation of response usually occurs in the second week of treatment. However, these treatment effects can sometimes be more severe (see section 4.8). In case of severe discomfort during treatment or for skin reactions lasting more than 4 weeks, symptomatic treatment (such as emollient or topical corticosteroids) should be offered (see section 4.2).

Occlusive dressing may increase inflammatory reactions of the skin.

Ophthalmic Adverse Reactions

Corneal and conjunctival disorders have occurred with topical 5-FU. Avoid application to the periocular area. To avoid transfer of the drug into the eyes and/or contact lenses and to the periocular area, patients should wash hands well after applying Tolak. If accidental exposure occurs, the patient should flush eye(s) with large amounts of water.

Hypersensitivity Reactions

Allergic contact dermatitis (delayed type hypersensitivity reaction) has been noted for topical 5-FU drugs. Delayed type hypersensitivity should be suspected in the event of severe pruritus or eczema at the application site or at a distant site.

Although the potential for a delayed hypersensitivity reaction to 5-FU exists, patch testing to confirm hypersensitivity may be inconclusive.

Photosensitivity

Topical 5-FU is associated with photosensitivity reactions. Exposure to ultraviolet rays including sunlight, sun lamps, and tanning beds should be avoided during treatment with Tolak.

Dihydropyrimidine dehydrogenase (DPD) deficiency

Significant systemic drug toxicity is unlikely via percutaneous absorption of fluorouracil when Tolak is administered as per the approved prescribing information. However, the likelihood of this is increased if the product is used on skin areas in which the barrier function is impaired (e.g. cuts), if the product is applied under an occlusive dressing, and/or in individuals with deficiency in dihydropyrimidine dehydrogenase (DPD). DPD is a key enzyme involved in metabolising and eliminating fluorouracil. Determination of DPD activity may be considered where systemic drug toxicity is confirmed or suspected. There have been reports of increased toxicity in patients who have reduced activity of the enzyme dihydropyrimidine dehydrogenase. In the event of suspected systemic drug toxicity, Tolak treatment should be stopped.

Patients with a known DPD deficiency should be intensively monitored for signs and symptoms of systemic toxicity during treatment with topical 5-FU.

Treatment with the antiviral nucleoside analogues Brivudine or sorivudine and topical cutaneous application of Tolak should be separated by an interval of at least four weeks.

Tolak contains:

- Butylhydroxytoluene (E 321) which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

- Cetyl alcohol and stearyl alcohol which may cause local skin reactions (e.g. contact dermatitis)

- Methyl parahydroxybenzoate (E 218) and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed)

4.5 Interaction with other medicinal products and other forms of interaction

The antiviral nucleoside analogues brivudine and sorivudine are potent inhibitors of DPD, metabolising enzyme of 5-FU (see Section 4.4). The concomitant use of these drugs with Tolak is contraindicated (See Section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of topical 5-FU in pregnant women. Studies in animals have shown that 5-FU is teratogenic (see section 5.3).

The potential risk for humans is unknown, hence Tolak must not be used during pregnancy (see section 4.3).

If a pregnancy occurs during treatment, the treatment must be interrupted, and the patient should be advised about the risk for the child of adverse effects associated with the treatment, and genetic counselling is recommended.

Contraception in males and females

Due to the genotoxic potential of fluorouracil, women of childbearing potential should not become pregnant during topical 5-FU therapy and must use an effective method of contraception during treatment with 5-FU therapy and for 6 months following completion of treatment.

Men must use an effective method of contraception and not father a child during treatment with 5-FU therapy and for 3 months following completion of treatment.

Breast-feeding

No information is available on the excretion of 5-FU into breast milk. Studies in animals have shown the 5-FU is teratogenic (see section 5.3). A risk to the suckling child cannot be excluded, so Tolak must not be used in nursing mothers (see section 4.3). If use during breastfeeding is absolutely necessary, breastfeeding must be discontinued.

Fertility

No clinical data in humans are available on the effects of topical 5-FU on fertility.

Experiments in various species revealed an impairment of the fertility and reproductive performance of systemic 5-FU. The use of topical 5-FU may impair female and male fertility.

Topical 5-FU is not recommended in women and men attempting to have a child.

4.7 Effects on ability to drive and use machines

It is unlikely that treatment will have any effect on the ability to drive and use machines when used according to the dosage instructions.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported events in subjects treated with Tolak in the primary clinical studies were application site reactions. An evaluation of application site tolerability was performed in the primary clinical studies (see section 5.1). Local reactions related to tolerability, associated with the pharmacological action of 5-FU included erythema, scaling/dryness, oedema, crusting, erosions, stinging/burning, and pruritus with an incidence of 62% to 99% by symptom. These local reactions were mild with an incidence of 17% to 37% by symptom, moderate with an incidence of 22% to 44% by symptom and severe with an incidence of 6% to 38% by symptom. They were transient with a peak at 4 weeks of treatment and resolved within 2-4 weeks after the end of treatment (see also normal pattern of response in section 4.4).

Aside from application site reactions, insomnia, nasal discomfort, pharyngitis, nausea, periorbital oedema, impetigo, rash, and lip blister were reported at a frequency below 1%.

Tabulated list of adverse reactions

The following table gives the adverse reactions reported in AK patients treated with Tolak once daily for 4 weeks during the primary clinical studies and reported spontaneously.

Their frequency is defined using the following conventions: 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).

System Organ Class	Preferred MedDRA terms *Frequency*		
	Common	**Uncommon**	**Not known**
Infections and infestations		Impetigo Pharyngitis	
Immune system disorders			Hypersensitivity reactions
Psychiatric disorders		Insomnia	
Eye disorders	Eye irritation	Eye swelling Periorbital oedema Lacrimation increased	
Respiratory, thoracic and mediastinal disorders		Nasal discomfort	
Gastrointestinal disorders		Lip blister Nausea	
Skin and subcutaneous tissue disorders		Rash	
General disorders and administration site conditions	Application site disorders: - Irritation - pain - reaction - erythema - pruritus - inflammation - oedema	Application site disorders: - haemorrage - erosion - dermatitis - discomfort - dryness - paraesthesia - photosensitivity reaction	

Description of selected adverse reactions

Hypersensitivity reactions

Although no case has been reported in the primary clinical trials of Tolak, allergic contact dermatitis (delayed type hypersensitivity reaction) has been reported with topical 5-FU drugs and with Tolak since first marketing authorization.

Photosensitivity

Topical 5-FU is associated with photosensitivity reactions including severe sunburn. Photosensitivity reaction was reported in one subject (0.3%) in the primary clinical studies of Tolak. It should be noted that photosensitivity reaction was also reported by a subject in the vehicle group.

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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

When applied on the skin as recommended, systemic intoxication with 5-FU is unlikely. Application of significantly higher doses than recommended may result in an increase of frequency of reactions at the application site and their severity.

There is no known clinical case of accidental ingestion of Tolak, however if this occurs signs of 5-FU overdosage may include nausea, vomiting, diarrhea and stomatitis.

Blood dyscrasias may occur in severe cases. Daily white cell counts should be performed and appropriate measures should be taken accordingly for the prevention of systemic infection.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pyrimidine analogues. ATC code: L01BC02

Tolak is a topical cystostatic preparation which exerts a beneficial therapeutic effect on neoplastic and pre-neoplastic skin lesions (previously not visible) while having less effect on normal cells.

Mechanism of Action

The active substance fluorouracil (FU) is a cytostatic agent that has an antimetabolite effect. Due to its structural similarity with the thymine (5-methyluracil) occurring in nucleic acids, FU prevents its formation and utilisation and in this way inhibits both DNA and RNA synthesis which results in growth inhibition.

Clinical efficacy and safety

The safety and efficacy of Tolak were evaluated in two primary, multi-centers, randomized, controlled studies (Trial 1 and trial 2) in subjects with at least 5 visible actinic keratosis lesions on the face, scalp, and/or ear (not exceeding 1 cm). Trial 1 compared Tolak to an already-approved active comparator (5-FU 5%) (twice daily) and a negative placebo control (vehicle). Trial 2 was a placebo-controlled study.

Application of the medication, once daily for 4 weeks, involved field treatment of the whole area of the face and/or ears and/or scalp where actinic keratosis lesions were identified at baseline. A high proportion of the patients in these studies applied Tolak cream on a large area of skin between 240 cm^2-961 cm^2 All efficacy endpoints were evaluated at 4 weeks off treatment. Subjects were all Caucasians with a mean age of approximately 68 years (33-89

years). The mean number of actinic keratosis was 14.4 and 16.2 (Trial 1) and 19.2 and 23.2 (Trial 2), in Tolak and Placebo group, respectively.

As shown in table 1, in both trials, superiority was demonstrated versus vehicle.
In trial 1, the difference in "100% complete clearance rate" of Tolak (5-FU 4%; once daily) (54.4%) minus active comparator (5-FU 5%; twice daily) (57.9%) was 3.5% with a lower 97.5% confidence limit of -11.11%. The difference in "75% complete clearance rate" of Tolak (80.5%) minus active comparator (80.2%) was 0.3% with a lower 97.5% confidence limit of -5.94% in the intention-to-treat population (with similar results in the per-protocol population).

Table 1: Subjects with 100 % and 75% clearing of actinic keratosis lesions at 4 weeks post-treatment

	Tolak Cream (5-FU 4%, once daily) % (n/N)	Vehicle % (n/N)	Active comparator (5-FU 5%; twice daily)
Subjects with 100% clearing of actinic keratosis lesions			
Trial 1	54.4% (192/353)	4.3% (3/70)	57.9% (202/349)
Trial 2	24% (12/50)	4% (2/50)	
Subjects with 75% clearing of actinic keratosis lesions			
Trial 1	80.5% (284/353)	7.1% (5/70)	80.2% (280/349)
Trial 2	74% (37/50)	10% (5/50)	

Safety of 4-week treatment Tolak was assessed up to 4 weeks post treatment, the majority of the reported adverse reactions and local skin responses were mild to moderate in intensity and resolved without sequelae.

Tolerability assessment
In addition to the collection of adverse reactions, the evaluation of application site tolerability was performed at every visit from Baseline through 4 weeks post- treatment (see section 4.8). In this respect, the primary clinical studies specifically monitored for local reactions related to tolerability, including erythema, scaling/dryness, edema, crusting, erosions, stinging/burning, and pruritus (see Table 2 below).

Table 2: Tolerability assessment in primary clinical studies (incidence of Application Site Reactions Occurring with 4 Weeks of Tolak Cream Treatment)

Parameter	**5-FU 4% Cream (N=369) n (%)**		active comparator (5-FU 5%) **(N=300) n (%)**		**5-FU 4% Vehicle Cream (N=116) n (%)**	
	Any grade	**Severe**	**Any grade**	**Severe**	**Any grade**	**Severe**

Erythema	364 (99%)	139 (38%)	293 (98%)	140 (47%)	83 (72%)	0 (0%)
Scaling/ Dryness	330 (89%)	71 (19%)	260 (87%)	75 (25%)	82 (71%)	0 (0%)
Crusting	295 (80%)	67 (18%)	258 (86%)	74 (25%)	19 (16%)	0 (0%)
Pruritus	286 (78%)	49 (13%)	258 (86%)	66 (22%)	26 (22%)	1 (1%)
Stinging/ Burning	280 (76%)	69 (19%)	260 (87%)	81 (27%)	27 (23%)	0 (0%)
Oedema	230 (62%)	21 (6%)	203 (68%)	24 (8%)	3 (3%)	0 (0%)
Erosions	228 (62%)	35 (9%)	199 (66%)	35 (12%)	5 (4%)	0 (0%)

Long term efficacy – lesion recurrence
After completing the two primary clinical studies, patients treated with Tolak were followed for 12 months for lesion recurrence. Of the 184 patients included in the analysis of recurrence, 83 (45.1%) patients remained clear 12 months after treatment and 101 (54.9%) patients had a recurrence within 12 months.

Pediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Tolak in all subsets of the pediatric population in the treatment of actinic keratosis (see section 4.2 for information on paediatric use).

Elderly population
Of the 403 subjects treated with Tolak in the phase III clinical trials, 204 subjects were 68 years and older while 199 subjects were below 68 years of age.

No overall differences in efficacy were observed between the two groups.

5.2 Pharmacokinetic properties

Absorption
5-FU shows low absorption following dermal application. In a systemic absorption study of topically applied Tolak 8 of 21 patients had undetectable (<1 ng/ml) levels of 5-FU. Among patients with detectable plasma 5-FU levels, the highest level of plasma 5-FU was generally observed at 1 hour post-dose and the observed maximum concentration ranged between 1.1 - 7.4 ng/mL.

Biotransformation
5-FU may be metabolised by catabolic or anabolic routes which are similar to those of endogenous uracil. The rate-limiting step in the metabolism of 5-FU is conversion to 5-6-dihydrofluorouracil by the enzyme DPD.

5.3 Preclinical safety data

No experimental data on the acute and sub-chronic toxicity of 5-FU after topical application are available.

Systemic administration in high doses of 5-FU indicates potential for teratogenic or embryotoxic effects in mice, rats, hamsters and monkeys.

Fertility studies with systemic 5-FU resulted in impairment of male fertility and in reduction of pregnancy rates in female rodents.

5-FU has no potential to induce point mutations either in bacteria or in mammalian cells *in vitro* or *in vivo*. 5-FU induced chromosome aberrations and/or micronuclei *in vitro* in several cell lines and was clastogenic after IP or oral administrations in mice and rats and after dermal application to mice. No evidence of carcinogenicity was found in several studies in rats or mice after intravenous or oral administration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stearoyl macrogolglycerides
butylhydroxytoluene (E 321)
cetyl alcohol
citric acid (E 330)
glycerol (E 422)
isopropyl myristate
methyl gluceth-10
methyl parahydroxybenzoate (E 218)
propyl parahydroxybenzoate
purified water
arachis oil, refined
sodium hydroxide (E 524)
stearic acid
stearyl alcohol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Shelf-life: 2 years

Shelf-life after first opening the immediate packaging: 4 weeks

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminum tube with membrane, internally coated with an epoxyphenolic lacquer, with a polypropylene piercing screw cap.

Pack sizes: 20 g and 40 g

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Pierre Fabre Limited

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RG2 6GP

8 MARKETING AUTHORISATION NUMBER(S)

PL 00603/0247

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/06/2024

10 DATE OF REVISION OF THE TEXT

29/10/2025