LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Tolak
(fluorouracil)

SE/H/1820/01/DC

This module reflects the scientific discussion for the approval of Tolak. The procedure was finalised on 2019-10-09. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Pierre Fabre Dermatologie has applied for a marketing authorisation for Tolak, 40 mg/g, cream. The active substance is fluorouracil. Fluorouracil is a cystostatic agent that by interference by thymine deficiency in DNA and RNA of rapidly growing cells that provokes unbalanced growth and death of the cell.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

PIP –Paediatric Investigation Plan

The PDCO/EMA has issued a Class waiver for paediatric population for Tolak in the treatment of actinic keratosis lesions of the face, ears, and/or scalp. Tolak is indicated in adults only.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Topical fluorouracil is an antimetabolite chemotherapy drug used for the treatment of dermatological conditions for nearly half a century.

As 5-FU is a drug substance with a well-established medical use in the treatment of several tumours in general (systemic administration) and dermatological pathologies (local application) in particular, all pharmacological data come from relevant scientific literature.

5-FU acts as a competitive inhibitor of thymidylate synthase. For that, it must first be metabolized to 5-fluoro-deoxyuridine monophosphate (FdUMP). FdUMP competitively inhibits the conversion of deoxyuridine monophosphate to deoxythymidine monophosphate; the resulting thymidine deficiency results in the inhibition of DNA synthesis. FdUMP can undergo further phosphorylation to be incorporated into DNA, likely contributing to the cytotoxicity of 5-FU. Fluorouracil may also be metabolized to floxuridine triphosphate and incorporated into RNA, contributing to the cytotoxicity by interfering with RNA splicing.

No safety pharmacology studies are reported. Safety information collected in studies with oral or parental administration showed effects in the CNS, CV system, respiratory system and gastrointestinal system. Considering the low systemic absorption after topical administration, such effects are unlikely to occur with this effect. The lack of dedicated safety pharmacology studies in animals is not of concern.

III.2 Pharmacokinetics

Pharmacokinetics of 5-FU is well documented in literature. Disposition and kinetics of the drug have been investigated and analyzed following administration of the drug through different routes. The administration of 5-FU through oral, intravenous infusion (bolus and continuous), intraperitoneal administration, and topical application, have provided insights on the systemic absorption from these various routes. Evaluation of 5-FU absorption is based on studies in human. In patients with actinic keratosis, 5-FU demonstrated only minimal systemic absorption following dermal application. At the end of 3 days, the total recovery ranged from 0.48% to 0.94%, indicating that only approximately 6% of the topical dose was absorbed systemically.

Considering the low systemic absorption after topical use, the systemic pharmacokinetics of 5-FU is of limited importance for the safety evaluation.

III.3 Toxicology

Toxicology data on fluorouracil are derived from studies with oral or parental administration of 5-FU, and the toxicity is as expected from the pharmacology with bone marrow and gastrointestinal tract as primary target organs. There are no toxicity studies with topical administration.

5-FU is clastogenic in vitro and in vivo after IP, oral or dermal administrations in mice and rats. Despite these observations, no evidence of carcinogenicity was in found in several studies in rats or mice after intravenous or oral administration. While a risk for carcinogenicity can not be excluded, based on the mode of action and the genotoxicity findings, it must be considered that the indication actinic keratosis is associated with a pronounced risk for progression to malignant tumors. The genotoxicity findings are therefore not a hindrance for the intended clinical use.

5-FU has been associated with developmental toxicity and teratogenicity in a number of animals. While the risk after topical administration is considered small, it is still agreed that a contraindication for use in pregnant women is adequate. There are other treatment options, and treatment can be delayed without detrimental consequences.

III.4 Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): fluorouracil					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	Log D_{ow} = -0.69			No PBT potential
PBT-statement:	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, based on actual market figures	0.070	µg/L			> 0.01 threshold
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	2	µg/L	*Anabaena flos-aquae*
Daphnia sp. Reproduction Test	OECD 211	NOEC	2.8	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	32	mg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	9.2	m/L	

Conclusions on studies:

Fluorouracil is not a PBT substance. Considering the above data, fluorouracil is not expected to pose a risk to the environment.

III.5 Discussion on the non-clinical aspects

There are no objections to an approval from a nonclinical point of view.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The general pharmacokinetic properties of topically applied 5-fluorouracil is briefly covered in the documentation submitted by the Applicant and supported by literature references. In addition, the Applicant has submitted a comparative PK study between Tolak and another 5% 5-FU cream, Efudix®.

Absorption

There is no absolute bioavailability data for Tolak, or for any other 5-fluorouracil cream. Available data however suggests low systemic absorption. In a published study from Levy et al (2001) where 10 patients received Efudix 1 g twice daily, around 0.2% of the given dose was retrieved in urine. As metabolism appears to be the major elimination pathway, an estimation of absolute bioavailability is however not possible based on the available data.

A comparative bioavailability study (HD-FU1206SA) has been submitted. The study was a phase II multiple dose open-label study to compare the steady state plasma concentrations of 5-FU after 28 days of application of 5-FU 4% cream (Tolak) and the comparator Efudix (5%) in patients with AK. Study medication was applied to entire area where the AK lesion was located (either cheek, chin/forehead, scalp or ear). Blood was drawn at baseline and at day 28, prior to dose and 1, 2, 4, 6, 8, 10, 12, 16 and 24 hours after dose. 5-FU was measured with LC-MS/MS.

20 subjects in the Tolak arm and 19 subjects in the Efudix arm completed the study and took their PK samples. 7 and 8 subjects in each arm had non-measurable drug concentrations 1 hour after dose. 12 h after dose no drug could be quantified in any subject. Among the subjects with measurable concentrations, the maximum drug concentration ranged between 1.6 and 13.2 ng/mL in the Efudix group, and 1.1 and 7.4 ng/ml in the Tolak group. Tmax was estimated at the first sampling point for most subjects.

Distribution and elimination

No data regarding distribution of 5-FU in the skin or target cells has been submitted in the current application. After systemic administration of 5-FU, the half-life is short (8-10 minutes according to the review Diasio 1989 referred to by the Applicant). The submitted review Diasio et al (1989) refers to that less than 10% of administered 5-FU is excreted unchanged. Metabolism appears to be important for 5-FU elimination.The metabolism of 5-FU is similar to that of endogenous uracil, both anabolic (activation by phosporylation) and catabolic. Catabolism catalysed by dipdihydropyrimidine dehydrogenase (DPD) appears to be a major metabolism pathway.

Special populations

The Applicant has not discussed PK in patients with renal or hepatic impairment or any other special populations and does not suggest any restrictions in the SmPC. This appears acceptable given the low fraction absorbed. Subjects with a genetic deficiency in the major metabolising enzyme dipdihydropyrimidine dehydrogenase (DPD) have been reported to experience severe toxicity after intravenous 5-FU administration. This risk is unknown for topically administered 5-FU with low systemic absorption. There is however a case report where a man treated for basal cell carcinoma with a 2-week course of topical 5% 5-FU cream (Efudix) twice daily

developed severe gastrointestinal and haemaological toxicity and was found to have a profound DPD deficiency. Based on this, the Applicant´s proposal to add a warning to the SmPC section 4.4 is accepted.

Interactions

No data available. The Applicant suggests that the risk of pharmacokinetic interactions would be low given the low systemic exposure. In general, this is agreed. In line with other dermal preparations of 5-fluorouracil, a contraindication is however added for co-treatment with bridovudin and sorivudin, known inhibitors of dipdihydropyrimidine dehydrogenase (DPD).

IV.2 Pharmacodynamics

5-FU is an antineoplastic, cytostatic agent which inhibits the enzyme thymidylate synthase resulting in inhibition of DNA synthesis leading to apoptosis and necrotic cell death of the actinic keratosis cells.

The clinical experience with 5-FU is extensive, both for systemic treatment of various neoplastic diseases and for topical treatment of AK. In Sweden, at present, there is no product containing solely 5-FU approved for treatment of AK, except the combination product Actikerall® which contains 5-FU 0.6% and salicylic acid 10%. However, 5-FU has been approved for treatment of AK (was deregistered in 1995), therefore there is a clinical knowledge in Sweden with the compound. The medicinal product Efudix® that contains 5-FU 5% is not marketed in Sweden however is available on a namned patient basis. In 2017, 4850 licenses on named patient basis in Sweden were approved for Efudix®, the majority for treatment of AK.

This product contains a novel vehicle with refined peanut oil, which according to the Applicant has hydrating properties able to ‘reduce the inflammation associated with application and improve acceptability by the patient while retaining adequate efficacy’. The 5-FU 4% cream has been developed to be applied once daily to the whole area of the face and/or ears and/or scalp where actinic keratosis lesions have been identified over a treatment period of 4 weeks.

IV.3 Clinical efficacy

The clinical development program for Tolak includes 8 Phase 1 through Phase 3 studies, that evaluated the safety and efficacy of 5-FU (see table below).

Table. Clinical Studies of 5-FU 4% Cream for Treatment of Actinic Keratosis

Study No.	Study Design	Study Population	Study Drug, Dose, and Frequency	No. Subjects	Duration of Drug Treatment	Completion Status / Location of Report
Controlled Primary Efficacy Studies in Adult Patients with AK						
HD-FUP3B-048	Phase III, randomised, investigator-blind, 4-arm, parallel group efficacy and safety study	Subjects ≥18 years, with AK of the face and/or ears and/or scalp	5-FU 4% Cream QD	353	4 weeks	Complete / Module 5.3.5.1
			5-FU 4% Vehicle Cream QD	70		
			Efudix® 5% cream BID	349		

Study No.	Study Design	Study Population	Study Drug, Dose, and Frequency	No. Subjects	Duration of Drug Treatment	Completion Status / Location of Report
			Comparator vehicle cream BID	69		
HD-FUP3S-049	Phase III, randomised, double-blind, 2-arm, parallel group safety and efficacy study	Subjects ≥18 years, with AK of the face and/or ears and/or scalp	5-FU 4% Cream QD	50	4 weeks	Complete / Module 5.3.5.1
			5-FU 4% Vehicle Cream QD	50		
Controlled Phase II Dose Ranging Study in Adult Patients with AK						
HD-FUDR-045	Phase II, randomised, investigator-blind, 6-arm, parallel group safety and efficacy study	Subjects ≥18 years, with AK of the face and/or ears and/or scalp	5-FU 4% Cream QD	20	4 weeks	Complete / Module 5.3.5.1
			5-FU 4% Cream BID	20	4 weeks	
			5-FU 4% Cream QD	20	2 weeks	
			5-FU 4% Cream BID	21	2 weeks	
			5-FU 4% Vehicle Cream BID	20	4 weeks	
			Efudix 5% Cream BID	20	4 weeks	
Controlled Phase II Pharmacokinetic Study in Adult Patients with AK						
HD-FU1206SA	Phase II, randomised, open-label, parallel group pharmacokinetic and safety study	Subjects ≥18 years, with AK of the face and/or ears and/or scalp	5-FU 4% Cream QD	21	4 weeks	Complete / Module 5.3.3.2
			Efudix 5% cream BID	22		
Long-Term Follow-up Study						
HD-FUP4LTS-050	Extension study of HD-FUP3B-048 and HD-FUP3S-049 to evaluate recurrence rates and long-term safety of 5-FU 4% cream	Subjects from Studies HD-FUP3B-048 and HD-FUP3S-049	5-FU 4% Cream QD	403	If retreated, 4 weeks	Complete / Module 5.3.5.2

The principle claim of efficacy is based on two pivotal Phase 3 studies, HD-FUP3B-048 and HD-FUP3S-049. Supportive evidence is provided by the Phase 2 study HD-FUP3B-045, and the long-term safety and recurrence study HD-FUP4LTS-050.

The endpoints in the Phase 3 studies HD-FUP3B-048 and HD-FUP3S-049 were identical. In study HD-FUP3B-048 the efficacy and safety of the 5-fluorouracil (5-FU) 4% cream and its cream vehicle was investigated. In addition, the active comparator Efudix® (5-FU 5% cream)

was used according its labelling, i.e. twice daily for 4 weeks and also its cream vehicle. In study HD-FUP3S-049 the efficacy and safety of the 5-FU 4% cream versus its vehicle was investigated.

Different durations of treatment (two versus four weeks), and once versus twice daily dosing, were studied in the Phase 2 study HD-FUDR-045. The results from this study supports the dosing regimen used in the Phase 3 trials; i.e., once daily application over a treatment period of 4 weeks and is proposed in this marketing authorisation application. The results of this study is briefly described and assessed below.

The Phase 3 study HD-FUP3B-048 is a fairly large study with approximately 350 subjects enrolled to each active group (5-FU 4% cream and Efudix® 5% cream) respectively, and approximately 70 subjects enrolled to each cream vehicle group. In study HD-FUP3S-049, 50 subjects were enrolled to the 5-FU 4% cream and its vehicle groups, respectively. The studies enrolled male and female patients 18 years of age or above having actinic keratosis lesions on the face, ears and scalp, which were eligible for treatment. There is no European guideline available for topical products indicated for treatment of actinic keratosis. Complete clearance of all AK lesions from the treated area has been historically used as the pre-defined endpoint for the measurement of the effectiveness of topical treatment in AK. More recently, partial clearance rates and reduction in lesion count have also been recognised as clinically relevant effectiveness measures in the treatment of AK.

The primary efficacy endpoint in all studies was the proportion of subjects with complete (100%) clearing of all AK lesions at 4 weeks off treatment (defined as “success”); subjects with lesions in the treated areas at this time point were identified as treatment failures. The time point of 4 weeks after completion of study medication has been historically chosen to allow local adverse events which are associated with the treatment effects of 5-FU (e.g., erythema, crusting) to subside. Thus, evaluation of AK lesions 4 weeks after completion of the treatment allows a more accurate evaluation of the residual lesions.

Secondary endpoints in all studies were: 1) the proportion of subjects in whom 75% of AK lesions have cleared at 4 weeks off treatment, the partial clearance rate (PCR); and 2) the percentage change in number of AK lesions from Baseline assessed at 4 weeks off treatment.

It is most likely that the secondary endpoint, the PCR, is a more clinically relevant outcome for a chronic disease with fluctuating course such as AK. When assessing clinical efficacy with PCR as endpoint, a 75% clearing of treated lesions is considered of clinical relevance.

A primary efficacy responder analyses was also performed by gender, age, ethnicity, race and number of lesions at baseline for the ITT population in the combined studies HD-FUP3B-048 and HD-FUP3S-049.

The Phase 3 long-term follow-up study HD-FUP4LTS-050 investigated mainly safety but also the recurrence of AK lesions 12 months after the end of the Phase 3 studies.

Efficacy data and additional analyses

In the pivotal Phase 3 studies, the majority of subjects were male. The mean age was slightly below 70 years of age. The absolute majority of subjects were Caucasians with Fitzpatrick skin type I-III. A larger percentage of subjects with Fitzpatrick skin type III was noted in study HD-FUP3S-049 compared with study HD-FUP3B-048. In addition, there was an imbalance in Fitzpatrick skin type in study HD-FUP3S-049 between treatment groups.

The studies were performed in the US. Actinic keratosis lesions are not considered to significantly differ between US and EU citizens, the results of the performed studies can therefore be extrapolated to EU conditions.

The mean number of AK lesions ranged from 14.4 to 16.2 in study HD-FUP3B-048, and from 19.2 to 23.2 in study HD-FUP3S-049. A higher percentage of subjects were determined to have severe AK (> 25 lesions), approximately 20% in study HD-FUP3S-049 versus 9%-14% of subjects in study HD-FUP3B-048. Thus there was a slight imbalance both between the studies regarding number of AK lesions and the severity of the disease. For more detailed information on demographic characteristics please see the Clinical Asssessment Report.

Study completion was high in all treatment groups. Adverse events were in the majority of cases reason for treatment discontinuation, which was noted in a higher frequency in the active, compared with vehicle treated groups as could be expected. The 5-FU 4% cream and the active comparator Efudix® 5% cream caused a similar number of treatment discontinuations due to adverse events.

Brief summary of results obtained in the Phase 2 study

The performed dose response study HD-FUDR-045, evaluated once versus twice daily treatments, and two versus four weeks total duration of treatment with the 5-FU 4% cream versus its cream vehicle. Efudix® 5% cream as active comparator plus its cream vehicle were dosed according to its labelling. Demographic characteristics were as could be expected for patients with AK; the majority were men in their 60ies. All were white/Caucasian with fair skin type with approximately 10 AK lesions.

The primary efficacy endpoint was the proportion of subjects with 100% clearing of AK lesions at 4 weeks off-treatment; the secondary efficacy endpoint was the proportion of subjects with 75% clearing of AK lesions and percent change in number of AK lesions.

Following treatment with 5-FU the number of AK lesions increases and peaks at the end of treatment, and then decreases which demonstrate the ability of 5-FU to reveal and treat also subclinical lesions (see table below). The reduction in AK lesion counts is more apparent 4-weeks off treatment compared with to 2-weeks off treatment. The mean number of AK lesions with 100% clearing decreased from 11.2 to 0.2 4-weeks off treatment for the dosing schedule proposed for marketing (once daily for four weeks). The 5-FU vehicle cream had no effect which is not to be expected, while the efficacy of the active comparator Efudix® was in the same range as for 5-FU cream. The results with the secondary efficacy parameters supported the result with the primary efficacy parameter.

Table. Efficacy of 5-FU 4% cream QD versus BID: Dose-ranging Study (HD-FUDR-045)

Efficacy Endpoint	Parameter	5-FU 4% cream 2 Weeks		5-FU 4% cream 4 Weeks	
		QD	BID	QD	BID
Primary: 100% Clearing of AK Lesions	**ITT Population**				
	N	20	21	20	20
	n (%)	12 (60%)	11 (52%)	16 (80%)	15 (75%)
	95% CI[1]	(36.1, 80.9)	(29.8, 74.3)	(56.3, 94.3)	(50.9, 91.3)
	PP Population				
	N	20	20	20	20
	n (%)	12 (60%)	11 (55%)	16 (80%)	15 (75%)
	95% CI[1]	(36.1, 80.9)	(31.5, 76.9)	(56.3, 94.3)	(50.9, 91.3)
Secondary: 75% Clearing of AK Lesions	**ITT Population**				
	N	20	21	20	20
	n (%)	17 (85%)	17 (81%)	20 (100%)	19 (95%)
	95% CI[1]	(62.1, 96.8)	(58.1, 94.6)	(83.2, 100.0)	(75.1, 99.9)
	PP Population				
	N	20	20	20	20
	n (%)	17 (85%)	17 (85%)	20 (100%)	19 (95%)
	95% CI[1]	(62.1, 96.8)	(58.1, 94.6)	(83.2, 100.0)	(75.1, 99.9)
Secondary: Percent Change in Number of AK Lesions	**ITT Population**				
	N	20	21	20	20
	Mean % Change	88.4	57.6	98.1	95.5
	Std. Deviation	18.3	137.4	4.2	9.1
	Range	43 to 100	-533 to 100[2]	88 to 100	70 to 100
	PP Population				
	N	20	20	20	20
	Mean % Change	88.4	87.2	98.1	95.5
	Std. Deviation	18.3	23.9	4.2	9.1
	Range	43 to 100	0 to 100	88 to 100	70 to 100

[1] 95% exact CIs for treatment success were computed using the Clopper-Pearson method.
[2] One subject (5-101) was excluded from the PP population as he missed 4-Weeks Off Treatment Visit. This subject also missed 2-Weeks Off Treatment Visit. Values for this subject correspond to the last observed non-missing value obtained.
Source: HD-FUDR-045 CSR Table 11.4.1.1 and 11.4.1.2

The results from this study support the dosing regimen used in the Phase 3 trials; i.e., once daily application over a treatment period of 4 weeks.

Summary of results obtained in the pivotal Phase 3 studies - Primary end-point

In the Phase 3 studies, the 5-FU 4% cream met the primary end-point and was significantly superior ($p<0.001$) compared with treatment with its cream vehicle. In study HD-FUP3B-048 (ITT population), which compared the treatment groups based on the proportion of subjects for whom all target lesions were judged to be clear 4 weeks post-treatment, statistically significant results were obtained for both 5-FU 4% cream (54.4% clear) and the active comparator Efudix ® 5% cream (57.9% clear) versus the 5-FU 4% cream vehicle (4.3% clear). It is in the

assessor's opinion not to be expected that AK lesions would disappear when treated with the cream vehicle. However, AK lesions can occasionally disappear without treatment.

Non-inferiority of the 5-FU 4% cream to Efudix® 5% cream was not demonstrated, the lower confidence limit fell 1.1 % below the required limit of -10%, supported by results of the per-protocol analyses. It was observed by the Applicant that the number of AK lesions was considerably higher (up to 90 lesions) in the performed study compared with the dose ranging study that was used to power study HD-FUP3B-048 (upper limit of 20 lesions). A post-hoc analysis was performed in which the upper limit of the number of lesions at baseline was limited to 25 lesions. This resulted in eliminating 44 subjects from the 5-FU 4% group and 33 subjects from the Efudix® 5% group. The resulting success rates were 57.6% (178/309 subjects) and 58.2% (184/316 subjects) for a difference of 0.6% and a lower confidence limit of -8.68%.

The post-hoc analysis was not pre-specified in the clinical study protocol or statistical analysis plan and, therefore, cannot be interpreted as a confirmation of non-inferiority of the test product in comparison to the reference product Efudix®. In addition, the performed analysis which excluded subjects by an ad-hoc criterion violates the randomization of the groups, and, hence, the causal interpretation of treatment effects. The company did not clearly describe the presumed role of lesion count at baseline, e.g. as a moderating treatment effect. The corresponding model of choice would have been a logistic regression with an interaction term between treatment and baseline lesion count. In addition to the role of baseline lesion counts as a moderator, a lack of statistical power may have contributed to the lack of significance of non-inferiority. It is expected that by choosing a more informative endpoint based on the actual lesion count (ie not a responder endpoint which lost information), additional statistical power could have been gained (see results confirming non-inferiority of secondary endpoint change from baseline below).

The sensitivity analyses using non-responder and responder imputation respectively, support the conclusions of the primary analysis.

In study HD-FUP3S-049, the result for the primary efficacy parameter, which compared the treatment groups on the proportion of subjects with 100% clear AK lesions, was statistically significant. In 24% of the subjects treated (12/50) with 5-FU 4% all lesions were cleared, versus 4% (2/50) with vehicle ($p < 0.004$). It is not to be expected that AK lesions can disappear when treated with a vehicle cream, but AK lesions may disappear by themselves.

Table. Proportion of Subjects with Success: Primary Efficacy Endpoint – 100% clearing of actinic keratosis lesions at 4-weeks off-treatment – studies HD-FUP3B-048 and HD-FUP3S-049 combined – treatment with 5-FU 4% cream and 5-FU 4% cream vehicle (ITT and PP populations)

Study	5-FU 4% cream % (n/N)	5-FU 4% vehicle cream % (n/N)	p-value 5-FU 4% cream vs. Vehicle[1]
ITT Population			
HD-FUP3B-048	54.4% (192/353)	4.3% (3/70)	<0.001
HD-FUP3S-049	24.0% (12/50)	4.0% (2/50)	0.004
Combined[2]	50.6% (204/403)	4.2% (5/120)	<0.001
PP Population			
HD-FUP3B-048	55.8% (182/326)	4.8% (3/63)	<0.001
HD-FUP3S-049	27.9% (12/43)	4.5% (2/44)	0.004
Combined[2]	52.6% (194/369)	4.7% (5/107)	<0.001

[1] Cochran-Mantel-Haenszel test, stratified by centre. No significant treatment by centre interactions were identified.
[2] Studies HD-FUP3B-048 and HD-FUP3S-049 combined.
Source: HD-FUP3B-048 CSR Table 14.2.3; HDFUP3S-049 CSR Table 14.2.3; Integrated Summary of Efficacy Tables 14.2.1.1.1, 14.2.1.2.1, and 14.2.3

Table. Proportion of Subjects with Success: Primary Efficacy Endpoint – 100% clearing of actinic keratosis lesions at 4-weeks off-treatment – studies HD-FUP3B-048 and HD-FUP3S-049 combined -5-FU 4% cream Efudix®

Study	5-FU 4% cream % (n/N)	Efudix® % (n/N)	Lower Limit 97.5% CI[1]
ITT Population			
HD-FUP3B-048	54.4% (192/353)	57.9% (202/349)	-11.11
HD-FUP3S-049	24.0% (12/50)	---	---
Combined[2]	50.6% (204/403)	---[3]	---
PP Population			
HD-FUP3B-048	55.8% (182/326)	60.6% (186/307)	-12.75
HD-FUP3S-049	27.9% (12/43)	---	---
Combined[2]	52.6% (194/369)	---[3]	---

[1] CI for the difference in treatment success rates (5-FU 4% cream minus Efudix®), computed using Wald's CI with Yate's continuity correction. Non-inferiority was established of the lower limit of the one-sided 97.5% CI was greater than -10%.
[2] Studies HD-FUP3B-048 and HD-FUP3S-049 combined.
[3] Results are not presented for this dose group for the combined studies because Study HD-FUP3S-049 did not have an Efudix® arm
Source: HD-FUP3B-048 CSR Table 14.2.3; HDFUP3S-049 CSR Table 14.2.3; Integrated Summary of Efficacy Tables 14.2.1.1.1, 14.2.1.2.1 and 14.2.3.

Although the result of the primary endpoint is statistically significant, the level of result was lower (24%) in study HD-FUP3S-049 compared with approximately 55% of treated subjects achieving 100% clear in study HD-FUP3B-048. The Applicant was asked to discuss the reason for the discrepancy in obtained results with the 5-FU 4% cream with the primary efficacy parameter. Since there was a difference in baseline disease severity between subjects in the two pivotal studies, the observed difference in obtained results of CCR may at least partly be attributed to the larger proportion of subjects with severe AK in study HD-FUP3S-049, than in study HD-FUP3B-048, although the difference in the number of subjects with severe AK

lesions is not assessed as large. Assessment of the secondary efficacy endpoints, which might be of higher relevance for the clinical situation, can be found below.

The sensitivity analysis using non-responder and responder imputation respectively, support the conclusions of the primary analysis.

Pivotal Phase 3 studies - Secondary end-points

The results for all secondary endpoints supported the results of the primary endpoint.

In study HD-FUP3B-048, 284 subjects (80.5%) were 75% clear in the 5-FU 4% group compared with 280 subjects (80.2%) in the Efudix® 5% group, and 5 subjects (7.1%) in the 5-FU 4% vehicle group. Non-inferiority of 5-FU 4% to Efudix® 5% and superiority to 5-FU 4% vehicle ($p<0.001$) were demonstrated for this secondary endpoint. Results of the per-protocol analyses supported the result obtained in the ITT population.

Lesion counts in the 5-FU 4% group decreased by 80.1% compared with 79.0% in the Efudix® 5% group, which demonstrated the non-inferiority of 5-FU 4% to Efudix® 5%. For the superiority analysis, lesion counts in the 5-FU 4% group decreased by 80.3% compared with 16.9% in the 5-FU 4% vehicle group. The difference between treatment groups was significantly difference ($p<0.001$) in favor of 5-FU 4%. The per-protocol analyses supported the result obtained in the ITT population.

The procedure for model selection for testing the secondary endpoint “Percent change from baseline” and the applied models were considered adequate (see comments above regarding calculation of lower limit of confidence interval). However, the median as a summary statistic to describe the percent change from baseline is not recommended, because of the assumed high number of ties. Therefore, the mean would have been preferred.

In study HD-FUP3S-049, the secondary endpoints; proportion of subjects for whom their actinic keratosis lesion were clear to 75%, and percent change from Baseline in total lesions both endpoints evaluated at 4-weeks off-treatment, overall supported the primary endpoint. 74% (37/50) subjects were had lesions that were 75% clear compared with 10% (5/50) subjects in the 5-FU 4% vehicle group. Lesion counts in the 5-FU 4% group decreased by 54% compared with 1.4% in the vehicle group.

Table. Proportion of Subjects with 75% Clearing of AK Lesions – studies HD-FUP3B-048 and HD-FUP3S-049 combined -5-FU 4% cream versus Efudix® versus 5-FU 4% vehicle cream

Study	5-FU 4% cream % (n/N)	Efudix % (n/N)	5-FU 4% vehicle cream % (n/N)	p-value 5-FU 4% cream vs. vehicle[1]	Lower Limit 97.5% CI[2]
ITT Population					
HD-FUP3B-048	80.5% (284/353)	80.2% (280/349)	7.1% (5/70)	<0.001	-5.94
HD-FUP3S-049	74.0% (37/50)	---	10.0% (5/50)	<0.001	---
Combined[3]	80.0% (321/403)	---[4]	8.3% (10/120)	<0.001	---
PP Population					
HD-FUP3B-048	82.5% (269/326)	85.0% (261/307)	7.9% (5/63)	<0.001	-8.56
HD-FUP3S-049	83.7% (36/43)	---	11.4% (5/44)	<0.001	---
Combined[3]	82.7% (305/369)	---[4]	9.3% (10/107)	<0.001	---

[1] Cochran-Mantel-Haenszel test, stratified by centre
[2] CI for the difference in treatment success rates (5-FU 4% cream minus Efudix®), computed using Wald's CI with Yate's continuity correction. Non-inferiority was established of the lower limit of the one-sided 97.5% CI was greater than -10%.
[3] Studies HD-FUP3B-048 and HD-FUP3S-049 combined.
Source: HD-FUP3B-048 CSR Table 14.2.4.1; HDFUP3S-049 CSR Table 14.2.4.1; HD-FUDR-045 CSR Table 11.4.1.2; Integrated Summary of Efficacy Tables 14.2.1.1.1, 14.2.1.2.1, and 14.2.4.1

Table. Proportion of Subjects with 75% Clearing of AK Lesions – studies HD-FUP3B-048 and HD-FUP3S-049 combined -5-FU 4% cream versus vehicle cream

Study	5-FU 4% cream % Change[1]	5-FU 4% Vehicle cream % Change	p-value 5-FU 4% cream vs. Vehicle[2]
ITT Population			
HD-FUP3B-048	80.3	16.9	<0.001
HD-FUP3S-049	54.0	1.4	<0.001
Combined[3]	75.8	15.7	<0.001
PP Population			
HD-FUP3B-048	83.3	16.9	<0.001
HD-FUP3S-049	69.2	3.3	<0.001
Combined[3]	80.8	14.5	<0.001

[1] Results presented for Studies HD-FUP3B-048, Study FUP3S-049, and the combined studies HD-FUP3B-048 and HD-FUP3S-049 are the least squares means from an ANOVA with factors of treatment and centre; results presented for Study HD-FUDR-045 are the means.
[2] Ranked ANOVA.
[3] Studies HD-FUP3B-048 and HD-FUP3S-049 combined.
Source: HD-FUP3B-048 CSR Table 14.2.4.2; HDFUP3S-049 CSR Table 14.2.4.2; HD-FUDR-045 CSR Table 11.4.1.2; Integrated Summary of Efficacy Table 14.2.4.2

The applicant has in the response to raised issue discussed the reason for the discrepancy in obtained results in study HD-FUPS-049 compared with study HD-FUPS-048. It is most likely that the secondary endpoint PCR, is a more clinically relevant outcome for a chronic disease with fluctuating course such as AK. When assessing clinical efficacy with PCR as endpoint, a 75% clearing of treated lesions is considered of clinical relevance which was assessed as secondary efficacy endpoint in the pivotal clinical studies. The overall percentage of subjects in the Tolak group with 75% clearing was 80.5% in study HD-FUP3B-048, and 74.0% in study HD-FUP3S-049.

The Applicant has also performed a supplementary analysis of the 75% PCR by baseline lesion count (5 to 10 lesions; 11 to 15 lesions; 16 to 20 lesions; 21 to 25 lesions; and >25 lesions) showing fairly similar results across all AK strata, suggesting that the number of AK lesions at baseline has fairly low influence on this endpoint. Also the endpoint mean percent change from baseline was less variable across all lesion strata, and therefore less affected by the number of AK at baseline than CCR across all lesion strata.

The model selection procedure and the applied model (ANOVA on ranks) are considered acceptable.

Analysis performed across trials

The Applicant has made an analysis across trial of the combined studies HD-FUP3B-048 and HD-FUP3S-049. The proportion of subjects with success for the primary efficacy endpoint showed results similar to those described above for the individual studies. The results of the secondary efficacy parameters overall supported the primary efficacy parameter.

Subgroup analysis

Subgroup analyses of success for the primary efficacy parameter (proportion of subjects with 100% clearing of AK lesions at 4 weeks off treatment) were performed by gender (male and female), age (<68.0 years and ≥68.0 years; 68 years being the median age of the cohort), ethnicity (Hispanic/Latino and not Hispanic/Latino), race (White; and Other), and number of lesions at baseline (5 to 10 lesions; 11 to 25 lesions; and >25 lesions) for the ITT population in the combined studies HD-FUP3B-048 and HD-FUP3S-049.

A greater percentage of females than males reported success for the primary efficacy endpoint with the 5-FU 4% cream while the difference between genders was not so pronounced for Efudix® 5% cream. Age had no effect on efficacy of the 5-FU 4% cream. In the subgroup analyses the success for the primary efficacy endpoint for 5-FU 4% cream seemed to be less in subjects with severe AK (>25 lesions) than in those with mild or moderate AK, compared with Efudix® that had similar level of treatment success in subgroups investigated. The Applicant was asked to speculate on the reasons for this discrepancy, and eventual implications on recommendations for use of the product. The partial clearance rate has been analysed by the Applicant in a larger number of AK lesion strata (5 to 10 lesions; 11 to 15 lesions; 16 to 20 lesions; 21 to 25 lesions; and >25 lesions) to supplement the first subgroup analysis. It is assessed that Tolak overall displays a consistent level of efficacy in all subjects irrespective of the number of lesions, and specific restrictions for use of Tolak based on disease severity is not needed.

Long-term follow-up studies

The long-term Phase 3 follow-up study HD-FUP4LTS-050, aimed at investigating the long-term safety of 5-FU 4% cream and to evaluate the recurrence of AK lesions. Subjects whose lesions were completely clear (a lesion count of 0) at the end of the previous studies (HD-FUP3S-048 & HD-FUP3S-049) and had no new AK lesions in the treated area(s) upon entry into Study HD-FUP4LTS-050 (baseline entry at the 6th month evaluation) were evaluated for recurrence of AK and safety after 12 months. The recurrence rate of AK lesions during the 12-month follow-up period after treatment with 5-FU 4% cream was 54.9%. This result is considered to be is the same range as for other products approved for treatment of AK lesions.

Conclusions on clinical efficacy

A significantly superior efficacy for Tolak (5-FU 4% cream) compared with vehicle cream was demonstrated for the primary endpoint in the two pivotal phase 3 studies HD-FUP3B-048 and HD-FUP3S-049. The secondary efficacy end-points and other endpoints supported the efficacy of Tolak. Overall, the efficacy documentation presented for 5-FU 4% cream is considered adequate.

The magnitude of efficacy demonstrated in the studies is in a similar range as for other products approved for topical treatment of actinic keratosis.

Tolak can be used on areas with several actinic keratosis lesions, for instance on the scalp or ears (field therapy) and no limitation on area of treatment is considered needed.

Tolak is proposed to be dosed once daily, which is considered an advantage for the product considering compliance of patients to treatment.

IV.4 Clinical safety

Topical 5-fluorouracil exerts its effect on neoplastic and pre-neoplastic skin lesions while having less effect on normal cells. It (frequently in 5 % preparations) has been used for several years in the treatment of actinic keratosis. The appearance of local reactions following topical administration for a limited period (usually 2-4 weeks) is common knowledge for clinicians prescribing the substance. Tolak is a topical 5-fluorouracil 4 % preparation. The applied indication is for the topical treatment of actinic keratosis lesions of the face, ears, and/or scalp in adults. The recommended dose is once daily application covering the whole area of the face and/or ears and/or scalp where AK lesions have been identified. The treatment has been evaluated in 3 parallel, randomised, controlled clinical trials: one dose-ranging phase II study-2 weeks versus 4 weeks and QD versus BID of dosing with 5-FU 4% cream and two primary phase III studies of 8 weeks (4 weeks of treatment and 4 weeks off treatment). Long-term exposure has been investigated through the conduct of a fourth trial in which subjects previously treated with 5-FU 4% cream in the two pivotal studies have been followed for a period of up to 12 months (study HD-FUP4LTS-050).

The evaluation of the safety of the 5-FU 4% cream was performed in 8 studies enrolling a total of 1429 subjects, of whom 829 were exposed to 5-FU 4% cream. Within all studies submitted in this application, a total of 505 subjects with AK were exposed to 5-FU 4% cream. A total of

391 subjects with AK were exposed to Efudix (fluorouracil 5 % cream) to provide comparative data.

The primary two studies addressed above (HD-FUP3B-048 and HD-FUP3S-049) enrolled a total of 941 subjects. Of these, 924 subjects were included in the safety population, i.e., the population on which the analysis of safety and tolerability was based. An overview of patients included in all studies (table 4) and in the pivotal, dose ranging and longterm studies (Table 10) is presented below.

Table 4: Overview of Subject Completion in All Studies Evaluating Safety in Humans

	5-FU 4% Cream			Efudex® 5% Cream	5-FU 4% Vehicle Cream	Comparator Vehicle Cream
Primary Clinical Studies (HD-FUP3B-048 and HD-FUP3S-049)						
Number of Subjects Enrolled	403			349	120	69
Number of Subjects who Completed the Study	386 (95.8%)			329 (94.3%)	113 (94.2%)	62 (89.9%)
Long-term Study (HD-FUP4LTS-050)						
Number of Subjects Enrolled	310			NA	NA	NA
Number of Subjects who Completed the Study	307 (99%)			NA	NA	NA
Dose-ranging Study (HD-FUDR-045)	***2 Weeks*** **QD /BID**	***4 Weeks*** **QD /BID**		***4 Weeks*** **BID**	***4 Weeks*** **BID**	NA
Number of Subjects Enrolled	20/21	20/20		20	20	NA
Number of Subjects who Completed the Study	20 (100%)/ 20 (95.2%)	20 (100%)/ 20 (100%)		20 (100%)	18 (90.0%)	NA
Pharmacokinetic Study (HD-FU1206SA)						
Number of Subjects Enrolled	21			22	NA	NA
Number of Subjects who Completed the Study	20 (95.2%)			19 (86.4%)	NA	NA
Special Safety Studies	**HDFU1106PT[1]**	**HDFU1206PA[1]**	**PRACSR05-1393[1]**	NA	NA	NA
Number of Subjects Enrolled	33	60[2]	231	NA	NA	NA
Number of Subjects who Completed the Study	33 (100%)	50 (83.3%)	209 (90.5%)	NA	NA	NA

NA=Not applicable. Treatment not administered.

[1] *All subjects received medications as indicated in Table 3, but are tallied only in the 5-FU 4% cream column*

[2] *66 subjects were enrolled, but only 60 subjects were treated*

Table 10: Overview of Extent of Exposure

	5-FU 4% Cream		Efudex® 5% Cream	5-FU 4% Vehicle Cream	Comparator Vehicle Cream
Primary Clinical Studies (HD-FUP3B-048 and HD-FUP3S-049)					
N subjects in assessment (Total)	394 (403)		337 (349)	120 (120)	65 (69)
Mean number of dosing days (SD)	26.4 (5.1)		25.8 (5.7)	28.1 (3.2)	28.0 (4.1)
Mean number of applications (SD)	26.1 (5.2)		50.8 (11.6)	28.0 (3.2)	55.8 (8.1)
Long Term Study (HD-FUP4LTS-050)					
N subjects	104		NA	NA	NA
Mean number of dosing days (SD)	27.8 (3.2)		NA	NA	NA
Mean number of applications (SD)	27.2 (3.3)		NA	NA	NA
Dose-ranging Study (HD-FUDR-045)	*2 Weeks*	*4 Weeks*	*4 Weeks*	*4 Weeks*	NA
	QD /BID	**QD /BID**	**BID**	**BID**	NA
N subjects	20 /21	20 /20	20	20	NA
Mean number of applications (SD)	14.6 (0.8) / 27.4 (2.8)	26.4 (4.7) / 52.0 (8.3)	47.4 (11.9)	56.3 (1.9)	NA

NA=Not applicable. Treatment not administered.
Mean number of dosing days not calculated in study HD-FUDR-045
ITT population for studies HD-FUP3B-048, HD-FUP3S-049 and HD-FUDR-045; Safety population for study HD-FUP4LTS-050
[1] 5-FU 4% vehicle cream for studies HD-FUP3B-048, HD-FUP3S-049 and HD-FUDR-045
[2] Comparator Vehicle for study HD-FUP3B-048

The extent of exposure is considered satisfactory considering that topical administration of fluorouracil for the treatment of actinic keratosis has been executed for many years and the safety profile from that perspective is rather well characterised. Of the 310 patients enrolled in study HD-FUP4LTS-050, a total of 104 patients (35.5%) were retreated with Tolak. The most frequently reported events overall following re-treatment were application site events, all of which were considered to be possibly related/related to treatment with Tolak. None of these events were reported as serious. The types of local events reported (erythema, irritation, pruritus) were similar to what was observed in studies HD-FUP3B-048 and HD-FUP3S-049 following initial treatment with Tolak. As local skin reactions were differently studied in study HD-FUP4LTS-050 a direct comparison between studies was difficult. Aside from local skin reactions, all adverse events but one (keratoacanthoma) were assessed by the investigators as unrelated to treatment with Tolak. There is a numerically higher number of skin neoplasms in the re-treated group but as most lesions according to the applicant appeared on other sites than those re-treated with Tolak therefore most likely are not a result of the application of Tolak.

AEs could be spontaneously reported by the subject, elicited during non-directive questioning by the investigator, and/or observed during physical examination of the subject.

Overall the safety profile is dominated by local reactions. Within the two pivotal studies application test sites were assessed for erythema, scaling/dryness, oedema, crusting, erosions, stinging/burning, and pruritus were made at every visit from baseline through 4 weeks post treatment.

The number and percentage of subjects who had evidence of erythema, scaling/dryness, crusting, pruritus, stinging/burning, oedema, and erosions at Week 4 of treatment (when the mean score for each parameter was at its most severe) are presented by intensity in Table 18 below.

Table 18: Local Tolerance Assessment at Week 4 of Treatment by Grade: Primary Clinical Studies (HD-FUP3B-048 and HD-FUP3S-049 Combined), Safety population

	5-FU 4%, Cream (N=397)	Efudex® 5% Cream (N=342)	5-FU 4%, Cream Vehicle (N=120)	Comparator Vehicle (N=65)
	n (%[1])	n (%)	n (%)	n (%)
Erythema				
None	5 (1%)	7 (2%)	33 (28%)	18 (29%)
Mild	64 (17%)	39 (13%)	75 (65%)	36 (57%)
Moderate	161 (44%)	114 (38%)	8 (7%)	8 (13%)
Severe	139 (38%)	140 (47%)	0 (0%)	1 (2%)
All grades[2]	364 (99%)	293 (98%)	83 (72%)	45 (71%)
Not reported	28	42	4	2
Scaling/Dryness				
None	39 (11%)	39 (13%)	34 (29%)	33 (52%)
Mild	125 (34%)	79 (26%)	70 (60%)	27 (43%)
Moderate	134 (36%)	106 (35%)	12 (10%)	2 (3%)
Severe	71 (19%)	75 (25%)	0 (0%)	1 (2%)
All grades[2]	330 (89%)	260 (87%)	82 (71%)	30 (48%)
Not reported	28	43	4	2
Crusting				
None	74 (20%)	42 (14%)	97 (84%)	53 (84%)
Mild	118 (32%)	82 (27%)	17 (15%)	8 (13%)
Moderate	110 (30%)	102 (34%)	2 (2%)	2 (3%)
Severe	67 (18%)	74 (25%)	0 (0%)	0 (0%)
All grades[2]	295 (80%)	258 (86%)	19 (16%)	10 (16%)
Not reported	28	42	4	2
Pruritus				
None	83 (22%)	42 (14%)	90 (78%)	45 (71%)
Mild	136 (37%)	91 (30%)	23 (20%)	17 (27%)
Moderate	101 (27%)	101 (34%)	2 (2%)	1 (2%)
Severe	49 (13%)	66 (22%)	1 (1%)	0 (0%)
All grades[2]	286 (78%)	258 (86%)	26 (22%)	18 (29%)
Not reported	28	42	4	2
Stinging/Burning				
None	89 (24%)	40 (13%)	89 (77%)	51 (81%)
Mild	103 (28%)	75 (25%)	24 (21%)	9 (14%)
Moderate	108 (29%)	104 (35%)	3 (3%)	3 (5%)
Severe	69 (19%)	81 (27%)	0 (0%)	0 (0%)
All grades[2]	280 (76%)	260 (87%)	27 (23%)	12 (19%)
Not reported	28	42	4	2
Oedema				
None	139 (38%)	97 (32%)	113 (97%)	58 (92%)
Mild	128 (35%)	96 (32%)	3 (3%)	3 (5%)
Moderate	81 (22%)	83 (28%)	0 (0%)	2 (3%)
Severe	21 (6%)	24 (8%)	0 (0%)	0 (0%)
All grades[2]	230 (62%)	203 (68%)	3 (3%)	5 (8%)
Not reported	28	42	4	2

	5-FU 4%, Cream (N=397)	Efudex® 5% Cream (N=342)	5-FU 4%, Cream Vehicle (N=120)	Comparator Vehicle (N=65)
	n (%[1])	n (%)	n (%)	n (%)
Erosions				
None	141 (38%)	101 (34%)	111 (96%)	59 (94%)
Mild	108 (29%)	86 (29%)	4 (3%)	2 (3%)
Moderate	85 (23%)	78 (26%)	1 (1%)	2 (3%)
Severe	35 (9%)	35 (12%)	0 (0%)	0(0%)
All grades[2]	228 (62%)	199 (66%)	5 (4%)	4 (6%)
Not reported	28	42	4	2

1. % is calculated using the number of subjects who reported AEs as the denominator (i.e. 369 in the 5-FU 4%, cream treatment group, 300 in the Efudex® 5% cream treatment groups, 116 in the 5-FU 4%, cream vehicle treatment group, and 63 in the comparator vehicle treatment group)
2. Mild, moderate, severe. Events were graded as follows: absent=0, mild=1, moderate=2, severe=3
Subjects in the 5-FU 4%, cream and 5-FU 4%, cream vehicle treatment groups applied study medication once daily.
Subjects in the Efudex® 5% cream and comparator vehicle treatment groups applied study medication twice daily.

Almost every patient experienced some local skin reaction of some severity grade, erythema being most common (99%) and oedema less common but still very common (62%). This is not surprising considering previous clinical experience with the topical use of this substance. Mean scores of the tolerability studies of the 5 FU 4% group were slightly lower and with less severe cases than the mean scores for the Efudix® group over the treatment phase. These findings of the assessment of local reactions of 5 FU 4% have been stated in section 4.8.of the SmPC. The presently proposed safety information of sections 4.3, 4.4 and 4.8 of the SmPC are considered acceptable.

In total, 48 non-fatal serious adverse events (SAEs) were reported by 30 subjects in the two primary clinical studies. Please see table 19 below

Table 19: Summary of Adverse Events, Safety Population

	5-FU 4% cream			Efudex® 5% Cream	5-FU 4% Vehicle Cream	Comparator Vehicle Cream
Primary Clinical Studies (HD-FUP3B-048 and HD-FUP3S-049)						
N	397			342	120	65
Subjects with 1 or more events, n (%)[1]	139 (35%)			122 (36%)	22 (18%)	13 (20%)
Number of Events	241			211	37	28
Number of SAEs, n (%)[2]	23 (10%)			7 (3%)	11 (30%)	8 (29%)
Long-term Study (HD-FUP4LTS-050)						
N	310			NA	NA	NA
Subjects with 1 or more events, n (%)[1]	57 (18.4%)			NA	NA	NA
Number of Events	102			NA	NA	NA
Number of SAEs, n (%)[2]	19 (18.6%)			NA	NA	NA
Dose-ranging Study (HD-FUDR-045)	*2 Weeks* **QD /BID**		*4 Weeks* **QD /BID**	*4 Weeks* **BID**	*4 Weeks* **BID**	NA
N	20 / 21		20 / 20	20	20	NA
Subjects with 1 or more events, n (%)[1]	20 (100%)/ 21 (100%)		20 (100%)/ 19 (95%)	20 (100%)	11 (55%)	NA
Number of Events	49 / 45		65 / 72	71	17	NA
Number of SAEs, n (%)[2]	1 (2%) / 0 (0%)		0 (0%) / 0 (0%)	0 (0%)	0 (0%)	NA
Pharmacokinetic Study (HD-FU1206SA)						
N	21			20	NA	NA
Subjects with 1 or more events, n (%)[1]	21 (100%)			22 (100%)	NA	NA
Number of Events	94			97	NA	NA
Number of SAEs, n (%)[2]	0 (0%)			0 (0%)	NA	NA
Special Safety Studies	**HD-FU1106PT[3]**	**HD-FU1206PA[3]**	**PRACS R05-1393[3]**			
N	33	60	231	NA	NA	NA
Subjects with 1 or more events, n (%)[1]	3 (9%)	24 (40%)	73 (32%)	NA	NA	NA
Number of Events	5	39	132	NA	NA	NA
Number of SAEs[2]	0	0	4	NA	NA	NA

Frequencies in studies HD-FUP3B-048 and HD-FUP3S-049 do not include the events evaluated as part of the tolerability assessments

NA=Not applicable. Treatment not administered.

[1] Proportion based on the number of subjects in the specific group

[2] Proportion based on the number of reported AEs

[3] All subjects received medications as indicated in Table 3, but are tallied only in the 5-FU 4% cream column

Of these, 22 SAEs occurred in 13 subjects receiving 5-FU 4% cream. Additionally, 15 subjects reported 19 SAEs. None of these SAEs were considered by the investigator to be related to 5-FU 4% cream: 1 SAE was considered as unlikely related and the remainder were considered as unrelated to 5-FU 4% cream. In the dose-ranging study, 1 SAE was reported and evaluated as not related to 5-FU 4%.

The most common System Organ Class (SOC) of reported SAEs was "Neoplasms benign, malignant and unspecified". When reviewing the presented narratives in this SOC of subjects

exposed to 5-FU 4% cream within the primary clinical studies the conclusion by the Applicant that these events seem unrelated to study medication is endorsed. In conclusion no serious systemic adverse events were reported in any of the performed studies that would indicate a new serious safety concern at the proposed clinical use. No case of pancytopenia, neutropenia or thrombocytopenia has been reported. An observed raised white blood cell count had a temporal association to a dental infection suggesting an association and two patients were reported with severe anemia already presented before exposure to study drug (in one case to the vehicle). These reactions were considered not related to the exposure to Tolak.

Conclusions on clinical safety

Tolak (5-fluorouracil 4 % cream) is applied topically once daily on AK lesions. Topical 5-fluorouracil has been used for several years in the treatment of actinic keratosis and the safety profile is considered well-known. The reported very common local skin reactions such as erythema, scaling/dryness, oedema, crusting, erosions, stinging/burning, and pruritus are not unexpected following topical administration of fluorouracil. Safety data from the pivotal studies included a comparison with vehicle as well as Efudix (5-fluorouracil 5%). Mean scores of a majority of local skin reactions of the 5 FU 4% group in the tolerability studies were slightly lower and with somewhat less severe cases than the mean scores for the Efudix® group over the treatment phase. There were no systemic SAEs evaluated as related to the topical treatments. Long-term exposure was investigated in subjects previously treated with 5-FU 4% cream in the two pivotal studies and followed for a period of up to 12 months. The extent of exposure is considered satisfactory considering that topical administration of fluorouracil for the treatment of actinic keratosis has been executed for many years and the safety profile from that perspective rather well characterised.

IV.5 Risk Management Plans

The MAH has submitted an updated risk management plan version 0.3 with data lock point 30-Oct-2017, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Tolak.

Safety specification

Non-clinical

The Applicant has submitted a presentation of and discussion around key findings from non-clinical studies.

Relevance to human usage; conclusion by the applicant:

Single-dose toxicity

A number of LD50 values are available in literature, although no investigation was performed using the dermal route.The acute LD50 published values are 81 to 245 mg/kg by IV administration, 115 to 230 via the oral route and 169 to 217 mg/kg after SC administration in mice or rats. In dogs, the LD50 by oral route is 30 mg/kg.

Repeat dose toxicity

When applied topically, fluorouracil has shown only low systemic absorption in humans. Studies of topically applied 14C-labeled fluorouracil showed a cutaneous absorption rate of

approximately 6% in humans [DILLAHA, 1965]. Therefore, because of this low penetration of fluorouracil across the skin, minimum systemic toxicological effects are expected in human use.

Genotoxicity
Fluorouracil is a pyrimidine analogue which interferes with the synthesis of DNA for which such genotoxic profile is expected. However, because of its low absorption after topical administration (range of 5 to 6 mg per daily dose of 100 mg), no significant impact on human use is expected.

Carcinogenicity
No adequate studies have been conducted in human to evaluate the carcinogenic potential of fluorouracil. Based on fluorouracil's mechanism of action, its low absorption when administered topically and target population, no implications for the human use are expected.

Developmental toxicity and teratogenicity
5-FU has not been adequately studied in animals to determine its effects on fertility and general reproductive performance. But some studies have suggested that high doses of systemically-administered 5-FU may impair fertility in rats and mice. Several studies following systemic administration of fluorouracil have indicated potential high dose teratogenic or embryotoxic effects in chick embryo, rats, hamsters and monkeys. The most common abnormalities were those of the tail and limb, as well as cleft palate. Low birth weight can also be associated with exposure to 5-FU. The exact mechanism of developmental toxicity and teratogenicity is not totally known but appears to correlate somewhat with thymidylate synthase inhibition in the rat. The risk of developmental toxicity and teratogenicity following dermal administration of 5-FU is likely to be low, due to the low systemic absorption and exposure to 5-FU following dermal administration. Nevertheless, there are only limited data from pregnant women exposed to fluorouracil (systemic or topical and, based on the severity of reported outcomes in isolated cases after systemic fluorouracil exposure in pregnancy (miscarriage, cleft lip/palate, cardiac defects), safety of topical fluorouracil during pregnancy represents an important potential risk.

Clinical
The summary of safety concerns as presented in version 0.3 of the RMP by the Applicant can be seen in the table below.

Summary of safety concerns	
Important identified risks	None
Important potential risks	Toxicity in patients with severe dihydropyrimidine dehydrogenase (DPD) deficiency
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Plans for post-authorisation efficacy studies

Not applicable as no post-authorisation efficacy studies are required.

Risk minimisation measures (RMM)

Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the Applicant.

Summary of activities in the risk management plan by medicinal product

Tolak 40mg/g (5-FU 4% cream) is indicated for the topical treatment of actinic keratosis lesions of the face, ears, and/or scalp. Tolak is indicated in adults only (see SmPC for the full indication).

It contains 5-fluorouracil as the active substance and it is given topically (40.0 mg of fluorouracil per gram (4%))

Important risks of Tolak 40mg/g (5-FU 4% cream), together with measures to minimise such risks and the proposed studies for learning more about Tolak 40mg/g (5-FU 4% cream)'s risks, are outlined below.

II.B Summary of important risks

Important potential risk 1- Toxicity in patients with severe dihydropyrimidine dehydrogenase (DPD) deficiency	
Evidence for linking the risk to the medicine	This potential risk is based on the known role of DPD in catabolism of fluorouracil and potential consequences for patients (partially) lacking this enzyme. The exaggerated fluorouracil toxicities may include mucositis, hair loss, diarrhoea, neutropenia, skin rash, and neurologic toxicities based on the experience with systemic fluorouracil. Evidence is supported by the data published in the scientific literature.
Risk factors and risk groups	Beside DPD deficiency itself, the risk factors include increased absorption of fluorouracil because of severe widespread erosion and ulceration of the skin surface, thinner skin than usual, low body mass, and prolonged exposure to the drug.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 4.2
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Summary of the RMP

The submitted Risk Management Plan, version 0.3 with data lock point 30-Oct-2017 is considered acceptable.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tolak has demonstrated a statistically significant efficacy in removal of actinic keratosis lesions on the face, ears and/or scalp. The efficacy results are considered robust and convincing and are in a similar range as for other products approved for topical treatment of actinic keratosis.

The safety profile involves mainly local adverse events. Performed studies indicate a slightly more favourable profile of these reactions compared to the active comparator (Efudix®). The safety specification of the RMP is acceptable.

5-FU has been used for topical treatment of AK since the 1960ies; the clinical experience of the active compound is extensive.

Overall, the efficacy and safety documentation presented for the 5-FU 4% cream is considered adequate.

The benefit/risk ratio is considered positive. The SmPC was mutually agreed upon during the DCP, and Tolak, 40 mg/g, cream, was recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Post approval commitments

Description	**Due date**
The applicant commits to adapt the product information and RMP once the on-going referral procedure addressing DPD deficiency (EMEA/H/A-31/1481) is finalised.	According to agreed time limits in the finalised EMEA/H/A-31/1481 referral procedure

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Tolak, 40 mg/g, cream, was positively finalised on 2019-10-09.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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