CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022259Orig1s000

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 15, 2015
Application Type and Number:	NDA 022259
Product Name and Strength:	Tolak (fluorouracil) Cream, 4%
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Hill Dermaceuticals
Panorama #:	2015-49986
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Team Leader:	Kendra Worthy, PharmD
DMEPA Associate Director:	Lubna Merchant, MS, PharmD

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Tolak, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

The Applicant previously submitted the proposed proprietary name, [redacted] (b) (4) for review in 2007. However, the Division of Drug Marketing, Advertising, and Communications (DDMAC) found the name, [redacted] (b) (4) unacceptable because the name minimizes the risks of the drug product in OSE Review #2007-2285, dated December 11, 2007. Subsequently, the applicant submitted the proposed proprietary name, Tolak, for review in 2008. DMEPA found the proposed name acceptable. However, the application received a Complete Response letter on June 22, 2009.

Thus, the Applicant re-submitted the name, Tolak, for review on February 25, 2015 during the current NDA review cycle.

1.2 PRODUCT INFORMATION

The following product information is provided in the February 25, 2015 proprietary name submission.

- Intended Pronunciation: tōl lāk
- Active Ingredient: Fluorouracil
- Indication of Use: Actinic Keratosis
- Route of Administration: Topical
- Dosage Form: Cream
- Strength: 4%
- Dose and Frequency: Apply once daily in an amount sufficient to cover the lesions of the face, ears, and/or scalp
- How Supplied: 40 g tubes
- Storage: 25°C (77°F), excursions permitted to 15°C – 30°C (59°F-86°F).
- Container and Closure Systems: n/a
- Reference Listed Drug: Efudex (NDA 016831)

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. DMEPA and the Division of Dermatology and Dental Products (DDDP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name[1].

2.2.2 Components of the Proposed Proprietary Name

The Applicant did not provide a derivation or intended meaning for the proposed name, Tolak in their submission. This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 FDA Name Simulation Studies

Ninety-three practitioners participated in DMEPA's prescription studies. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. One participant in the inpatient study erroneously documented another study name, (b) (4); however, upon further investigation the participant interpreted the study name, Tolak, correctly. Therefore, 65 participants interpreted the name, Tolak, correctly (outpatient n=30, voice n=1, inpatient n=34). Appendix B contains the results from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines at Initial Review

In response to the OSE, March 12, 2015 e-mail, the Division of Dermatology and Dental Products (DDDP) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

2.2.5 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Table 1 lists the number of names with the combined orthographic and phonetic score of ≥50% retrieved from our POCA search[2] organized as highly similar, moderately similar or low similarity for further evaluation.

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[1] USAN stem search conducted on March 24, 2015.

[2] POCA search conducted on April 30, 2015.

Table 1. POCA Search Results	Number of Names
Highly similar name pair: combined match percentage score ≥70%	2
Moderately similar name pair: combined match percentage score ≥50% to ≤ 69%	60
Low similarity name pair: combined match percentage score ≤49%	0

2.2.6 Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities

Our analysis of the 62 names contained in Table 1 determined that none of the names will pose a risk for confusion as described in Appendices C through H.

2.2.7 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Dermatology and Dental Products (DDDP) via e-mail on May 12, 2015. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the DDDP on May 12, 2015, they stated no additional concerns with the proposed proprietary name, Tolak.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have further questions or need clarifications, please contact Janet Anderson, OSE project manager, at 301-796-0675.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Tolak, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your February 25, 2015 submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. ***USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)***

   USAN Stems List contains all the recognized USAN stems.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html#).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. . For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNCE. OPDP or DNCE evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNCE provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [3]

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there medical and/or coined abbreviations in the proprietary name?**
	Proprietary names should not incorporate medical abbreviations (e.g., QD, BID, or others commonly used for prescription communication) or coined abbreviations that have no established meaning.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.

[3] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

Y/N	Is this proprietary name used for another product that does not share at least one common active ingredient?
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 50% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥50% to ≤ 69%.
- Low similarity: combined match percentage score ≤49%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names with overlapping or similar strengths or doses represent an area for concern for FDA. The dosage and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and it can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form, etc.) may be limited when the strength or dose overlaps. We review such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).
- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name.

These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair do not share a common strength or dose.			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	Y/N	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	Y/N	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	Y/N	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	Y/N	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥50% to ≤69%).

<table>
<tr><td>Step 1</td><td colspan="2">Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation.

For single strength products, also consider circumstances where the strength may not be expressed.

For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components.

To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion:
○ Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa.
○ Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity.
○ Similar sounding doses: 15 mg is similar in sound to 50 mg</td></tr>
<tr><td rowspan="2">Step 2</td><td colspan="2">Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names <u>with</u> overlapping or similar strengths or doses.</td></tr>
<tr><td>Orthographic Checklist (Y/N to each question)
• Do the names begin with different first letters?

Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.
• Are the lengths of the names dissimilar* when scripted?

*FDA considers the length of names different if the names differ by two or more letters.
• Considering variations in scripting of some letters (such as z and f), is there a different number or placement of upstroke/downstroke letters present in the names?
• Is there different number or placement of cross-stroke or dotted letters present in the names?
• Do the infixes of the name appear dissimilar when scripted?
• Do the suffixes of the names appear dissimilar when scripted?</td><td>Phonetic Checklist (Y/N to each question)
• Do the names have different number of syllables?
• Do the names have different syllabic stresses?
• Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
• Across a range of dialects, are the names consistently pronounced differently?</td></tr>
</table>

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤49%).

In most circumstances, these names are viewed as sufficiently different to minimize confusion. Exceptions to this would occur in circumstances where, for example, there are data that suggest a name with low similarity is nonetheless misinterpreted as a marketed product name in a prescription simulation study. In such instances, FDA would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Tolak Study (Conducted on 3/24/15)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: Tolak Apply to lesions once daily for 4 weeks Outpatient Prescription: Tolak UAD #1	Tolak Use as directed Dispense #1

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

As of Date 4/30/2015

250 People Received Study
93 People Responded

Study Name: Tolak

Total	30	29	34	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
(b) (4)	0	0	1	1
TOLAC	0	21	0	21
TOLACK	0	5	0	5
TOLAK	30	1	33	64
TOLAQ	0	1	0	1
TOLAX	0	1	0	1

Appendix C: Highly Similar Names (e.g., combined POCA score is ≥70%)

No.	Proposed name: Tolak Established name: fluorouracil Dosage form: Cram Strength(s): 4% Usual Dose: Apply once daily to the affected areas	POCA Score (%)	Orthographic and/or phonetic differences in the names sufficient to prevent confusion Other prevention of failure mode expected to minimize the risk of confusion between these two names.
1.	Tolak	100	Proposed name subject of this review.
2.	Terak	76	Orthographic: Tolak contains an additional up stroke letter 'l' that gives the name a different shape when scripted. Phonetic: The first syllables of this name pair sound different. Other: Discontinued product with only one branded equivalent available. The branded equivalent product ANDA is still active; however, as per the 2010 Annual Report (reporting period 06-Sep-2009 to 05-Sep-2010) this product is no longer marketed.

Appendix D: Moderately Similar Names (e.g., combined POCA score is ≥50% to ≤69%) with no overlap or numerical similarity in Strength and/or Dose

No.	Name	POCA Score (%)
3.	Tylox Note: Discontinued products with branded and generic equivalents available	53
4.	(b) (4) ***	52
5.	Ten-K Note: Discontinued products with branded and generic equivalents available	52
6.	Colace	51
7.	Etodolac	51
8.	Tiazac	50

Appendix E: Moderately Similar Names (e.g., combined POCA score is ≥50% to ≤69%) with overlap or numerical similarity in Strength and/or Dose

No.	Proposed name: Tolak Established name: fluorouracil Dosage form: Cram Strength(s): 4% Usual Dose: Apply once daily to the affected areas	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
9.	Talc	64	Orthographic: The suffixes of this name pair have sufficient orthographic differences. Phonetic: Tolak contains an extra syllable.
10.	Cholac	62	Orthographic: The prefixes and suffixes of this name pair have sufficient orthographic differences. Phonetic: The initial sounds 'T' vs. 'Ch' of this name pair sound different. Dose: Apply to affected area or UAD vs. xx mL or xx tsp
11.	Salac Note: Discontinued product with branded and generic equivalents available.	62	Orthographic: The suffixes of this name pair have sufficient orthographic differences. Phonetic: The first syllables of this name pair sound different.
12.	Tol-tab Note: Discontinued product with generic equivalents available.	62	Orthographic: The suffixes of this name pair have sufficient orthographic differences. Phonetic: The second syllables of this name pair sound different. Dose: Apply to affected area or UAD vs. xx tabs or xx mg

No.	Proposed name: Tolak Established name: fluorouracil Dosage form: Cram Strength(s): 4% Usual Dose: Apply once daily to the affected areas	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
13.	Gonak	57	Orthographic: The prefixes and infixes of this name pair have sufficient orthographic differences. Phonetic: The first syllables of this name pair sound different.
14.	Taltz***	54	Orthographic: The suffixes of this name pair have sufficient orthographic differences. Phonetic: Tolak contains an extra syllable. Dose: Apply to affected area or UAD vs. xx mg
15.	Alcalak	52	Orthographic: The length and prefixes of this name pair have sufficient orthographic differences. Phonetic: Alcalak contains an extra syllable. Dose: Apply to affected area or UAD vs. xx mg or xx tab
16.	Folate	52	Orthographic: The suffixes of this name pair have sufficient orthographic differences. Phonetic: The second syllables of this name pair sound different. Dose: Apply to affected area or UAD vs. xx tab

No.	Proposed name: Tolak Established name: fluorouracil Dosage form: Cram Strength(s): 4% Usual Dose: Apply once daily to the affected areas	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
17.	Folex Note: Discontinued product with generic equivalents available.	52	Orthographic: The suffixes of this name pair have sufficient orthographic differences. Phonetic: The second syllables of this name pair sound different. Dose: Apply to affected area or UAD vs. xx mg
18.	Poly D	52	Orthographic: The suffixes of this name pair have sufficient orthographic differences. Phonetic: The second syllables of this name pair sound different. Poly D contains an extra syllable.
19.	Salic-2	52	Orthographic: The suffixes of this name pair have sufficient orthographic differences. Phonetic: The first syllables of this name pair sound different. Salic-2 contains an extra syllable.
20.	Thiola	52	Orthographic: The prefixes and suffixes of this name pair have sufficient orthographic differences. Phonetic: Thiola contains an extra syllable.

No.	Proposed name: Tolak Established name: fluorouracil Dosage form: Cram Strength(s): 4% Usual Dose: Apply once daily to the affected areas	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
21.	Trilog Note: Discontinued product with a branded equivalent available.	52	Orthographic: The suffixes of this name pair have sufficient orthographic differences. Phonetic: The names sound different. Dose: Apply to affected area or UAD vs. xx mg
22.	Teladar Note: Discontinued product with generic equivalents available.	51	Orthographic: The length and suffixes of this name pair have sufficient orthographic differences. Phonetic: Teladar contains an extra syllable.
23.	Tenake Note: Discontinued product with branded and generic equivalents available.	50	Orthographic: The infixes of this name pair have sufficient orthographic differences. Phonetic: The first syllables of this name pair sound different. Dose: Apply to affected area or UAD vs. xx mg or xx tabs or xx caps
24.	Today	50	Orthographic: The suffixes of this name pair have sufficient orthographic differences. Phonetic: The second syllables of this name pair sound different. Dose: Apply to affected area or UAD vs. insert one sponge intravaginally

No.	Proposed name: Tolak Established name: fluorouracil Dosage form: Cram Strength(s): 4% Usual Dose: Apply once daily to the affected areas	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
25.	Tusso-C Note: Discontinued product with a branded equivalent available.	50	Orthographic: The infixes of this name pair have sufficient orthographic differences. Phonetic: The names sound different. Tusso-C contains an extra syllable. Dose: Apply to affected area or UAD vs. xx mL or xx tsp

Appendix F: Low Similarity Names (e.g., combined POCA score is ≤49%)

N/A

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Name	POCA Score (%)	Failure preventions
26.	Teslac	64	Discontinued product with no generic equivalents available. NDA 016118 was withdrawn FR effective 7/8/11. NDA 016119 was withdrawn FR effective 8/20/10/
27.	Tylan	61	This is an animal drug.
28.	Colax	60	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.

No.	Name	POCA Score (%)	Failure preventions
29.	Tora	59	Discontinued product with no generic equivalents available. ANDA 084135 was withdrawn FR effective 5/12/1994.
30.	Teva-cc	58	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
31.	Tilade	58	Discontinued product with no generic equivalents available.
32.	(b) (4) ***	57	Proposed name found conditionally acceptable by DMEPA for IND (b) (4); however, the IND status is Inactive as of (b) (4).
33.	Tri-K	57	Discontinued product with no generic equivalents available.
34.	Tumil-K	56	This is an animal drug.
35.	Tuss-LA	56	Discontinued product with no generic equivalents available.
36.	Solis	55	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
37.	Tolnate	55	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
38.	Tolazil	54	

No.	Name	POCA Score (%)	Failure preventions
39.	Zorac	54	International drug name for tazarotene in Europe.
40.	(b) (4) ***	53	Proposed name found unacceptable by DMEPA for NDA (b) (4); however, the NDA status is Withdrawn as of (b) (4).
41.	Cholan	52	Discontinued product with no generic equivalents available.
42.	Talacen	51	Discontinued product with no generic equivalents available. NDA 018458 was withdrawn FR effective 8/19/2013.
43.	Tycolet	50	Discontinued product with no generic equivalents available. ANDA 089385 was withdrawn FR effective 3/5/1993.

Appendix H: Names not likely to be confused due to notable spelling, orthographic and phonetic differences.

No.	Name	POCA Score (%)
44.	SULPAK	60
45.	CO-LAV	58
46.	ETOPLAC	56
47.	STOOL-LAX	56
48.	CYTRA-K	54
49.	QUILIK	54
50.	APLEEK	53
51.	300 PRO LA	52
52.	CATULAC	52

No.	Name	POCA Score (%)
53.	Q-LAX	52
54.	SLOW-K	52
55.	GLU-K	51
56.	KETEK	51
57.	CALAN	50
58.	COLDEC	50
59.	DOLORAC	50
60.	SHELLAC	50
61.	VETA-K1	50
62.	XOLEX	50

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/s/

CARLOS M MENA-GRILLASCA
05/15/2015

KENDRA C WORTHY
05/18/2015

LUBNA A MERCHANT
05/18/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 16, 2008
To:	Susan Walker, M.D., Director Division of Dermatology and Dental Products, HFD-540
Through:	Linda Kim-Jung, Pharm.D., Team Leader Denise Toyer, Pharm.D., Deputy Director Division of Medication Error Prevention, HFD-420
From:	Tara Turner, Pharm.D., Safety Evaluator Division of Medication Error Prevention, HFD-420
Subject:	Proprietary Name, Label, and Labeling Review
Drug Name(s):	Tolak (Fluorouracil) Cream, 4%
Application Type/Number:	NDA # 22-259
Applicant:	Hill Dermaceuticals, Inc.
OSE RCM #:	2008-37

***** This document contains proprietary and confidential information that should not be released to the public.*****

CONTENTS

EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Tolak, has some similarity to other proprietary and established drug names, but the findings of the FMEA indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. The Division of Medication Error Prevention does not object to the use of the proprietary name Tolak for this product at this time.

However, the results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed carton and container labels are vulnerable to confusion that could lead to medication errors. The Division of Medication Error Prevention believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review. Additionally, if the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to a request from the Division of Dermatology and Dental Products (HFD-540) for assessment of the proprietary name, Tolak, regarding potential name confusion with other proprietary or established drug names. Tolak is the second name submitted by the applicant. Previously, DDMAC objected to the applicant's first proposed name, (b) (4) and the review division concurred (see OSE review 2007-2285 dated December 11, 2007).

Additionally, container labels, carton and insert labeling were provided for evaluation to identify areas that could lead to medication errors.

1.2 REGULATORY HISTORY

The Tolak application is a 505(b)(2) NDA. The reference listed drug is Efudex Cream, 5%, which was approved on July 29, 1970 under NDA 16-831. Efudex is also available as a topical solution in strengths of 2% and 5%. Efudex is indicated for the topical treatment of multiple actinic or solar keratoses. The 5% strength may also be used to treat superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites.

1.3 PRODUCT INFORMATION

Tolak (fluorouracil) Cream is indicated for the topical treatment of actinic keratosis lesions of the face, ears, and scalp. It should be applied once daily in an amount sufficient to cover the lesions with a thin film, using the fingertips to gently massage the medication uniformly into the skin. Tolak should be applied for a period of 4 weeks as tolerated.

Tolak is available in 40 gram tubes containing fluorouracil 4% in a cream base.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Container, Carton Label, and Insert Label Risk Assessment). The primary focus for both of the assessments is to identify and remedy potential sources

of medication error prior to drug approval. We define a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Tolak, and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, and ANDA products currently under review by the Agency.

For the proprietary name, Tolak, the medication error staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). We also conduct internal CDER prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.4).

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [2] FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. We use the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the Staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, we consider the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[3]

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[3] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

2.1.1 Search Criteria

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'T' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[4,5]

To identify drug names that may look similar to Tolak, the Staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (five letters), upstrokes (three: upper case letter 'T', lower case letter 'l' and lower case letter 'k'), downstokes (none), cross-strokes (one, lower case 't') and dotted letters (none). Additionally, several letters in Tolak may be vulnerable to ambiguity when scripted, including the upper case letter 'T' may appear as an upper case 'F', 'L', or 'R'; lower case 'o' may appear as a lower case 'e', 'a', or 'u'; lower case 'l' may appear as a lower case 'e' or 'b'; lower case 'a' may appear as a lower case 'c', 'ce', 'ci', 'e', or 'u'; lower case 'k' may appear as a lower case 'h' or 'b'. As such, the Staff also consider these alternate appearances when identifying drug names that may look similar to Tolak.

When searching to identify potential names that may sound similar to Tolak, the Medication Error Staff search for names with similar number of syllables (2), stresses (TOL-ak or tol-AK), and placement of vowel and consonant sounds. In addition, several letters in Tolak may be subject to interpretation when spoken, including the letter 'T' may be interpreted as 'D'; the letter 'o' may be interpreted as 'a'; or the letter 'k' may be interpreted as 'c'. The Sponsor's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting For this review, the Medication Error Staff were provided with the following information about the proposed product: the proposed proprietary name (Tolak), the established name (fluorouracil), proposed indication (topical treatment of actinic keratosis lesions of the face, ears, and scalp), strength (4%), dose (apply an amount sufficient to cover the lesions with a thin film), frequency of administration (daily), route (topical), and dosage form (cream). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff generally take into consideration.

Lastly, the Medication Error Staff also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the Medication Error Staff provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and information sources

The proposed proprietary name, Tolak, was provided to the medication error staff to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Tolak using the criteria outlined

[4] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[5] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the Medication Error Staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the Medication Error Staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held to gather CDER professional opinions on the safety of the product and the proprietary name, Tolak. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of Medication Error Prevention Staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

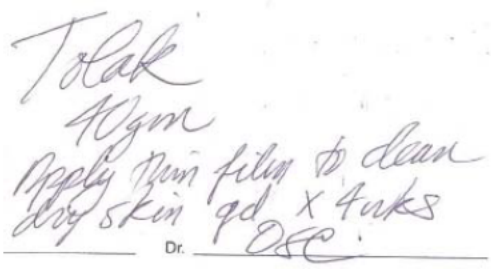
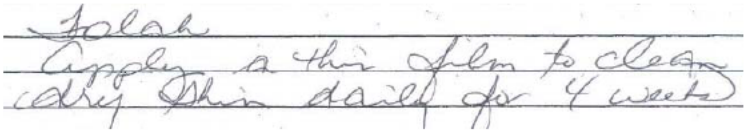
The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 CDER Prescription analysis studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Tolak with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ a total of 123 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterepreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of Tolak in handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one prescription is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to the medication error staff.

Figure 1. Tolak Study (conducted on February 7, 2008)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
Outpatient Prescription:  	Tolak 40 gram tube Apply in a thin film to clean dry skin daily for 4 weeks
Inpatient Medication Order :  	

2.1.3 Adverse Event Reporting System (AERS)

On November 29, 2007, we searched the FDA Adverse Event Reporting System (AERS) to retrieve any medication errors relating to the currently marketed topical fluorouracil products (Carac, Efudex, and Fluoroplex). AERS was searched using the trade name terms "*Carac", "Efudex", "Fluoroplex", and "fluorouracil",* active ingredient term *"fluorouracil",* as well as the verbatim terms "*Carac", "Efudex", "Fluoroplex", and "fluorouracil"* with the MedDRA high level group term "Medication Errors" and preferred term *"Pharmaceutical Product Complaint"*. The search was limited to cutaneous and topical routes of administration.

2.1.4 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, we seek to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective then remedies available in the post-approval phase.

[6] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Tolak convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Tolak to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking "Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?" The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

The Division of Medication Error Prevention will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. We identify that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

In the event that we object to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to use the name, while we will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then we will not object to the use of the proprietary name. If any of these conditions are met, then we will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Sponsor; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the IOM, WHO, JCAHO, and ISMP, who have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, we contend that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Sponsor, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Sponsor's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, we believe that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If we object to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. We are likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for us to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so we may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[7]

[7] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

Because Medication Error Prevention staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on November 19, 2007 the following label and labeling for our review (see Appendices G, H for images):

- Container Label: 40 g
- Carton Labeling: 40 g (b) (4) sides)
- Insert Labeling (no image)

Please note that the labels and labeling that the Applicant submitted contains their initial proposed proprietary name, (b) (4) which was found unacceptable by DDMAC with the review division's concurrence. We were informed by the review division that the Applicant plans to use the same labels and labeling, substituting Tolak as the proprietary name.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and information sources

We conducted a search of the internet, several standard published databases and information sources (see Section 7 References) for existing drug names which sound-alike or look-alike to Tolak to a degree where potential confusion between drug names could occur and result in medication errors in the usual clinical practice settings. In total, twenty-four names were identified as having some similarity to the name Tolak.

Nine of the twenty-four names were thought to look like Tolak, which include: Folate, Tubex, Lobac, Taxol, Zoloft, Foltx, Tarka, Talc, and Tolcapone. Three of the twenty-four names, Tolectin, Penlac, and Tiazac, were thought to sound like Tolak. The remaining twelve names, Tylox, Tolaz, Colax, Tolerex, Teslac, Terak, (b) (4) ***, Folex, Folic Acid, Tolax, Toilax, and Cholac, were thought to look and sound similar to Tolak.

Additionally, the Division of Medication Error Prevention did not identify any USAN stems in the name, Tolak, as of February 19, 2008.

3.1.2 Expert panel discussion

The Expert Panel reviewed the pool of names identified by Medication Error Prevention staff (see section 3.1.1. above). Additionally, the Expert Panel indicated that "Tol" is an abbreviation for tolerate and "AK" is an abbreviation for Actinic Keratosis.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.1.3 CDER Prescription analysis studies

A total of 29 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. Less than half of the participants (n=13) interpreted the name correctly as "Tolak", with correct interpretation occurring more frequently in the written outpatient study. The remainder of the responses misinterpreted the drug name. The majority of misinterpretations occurred in the written

inpatient study, with the capital 'T' in Tolak reported as capital 'F' by 6 respondents and the lower case 'k' was misinterpreted as 'h' by 10 respondents. Additionally, there was one respondent in the inpatient study who interpreted the first letter of the name as either 'T' or 'F'. In the verbal prescription study all 3 respondents misinterpreted the 'k' as 'c'. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 Adverse Event Reporting System (AERS)

The search of the Adverse Event Reporting System retrieved six medication error reports. Four cases involve use of the wrong dose resulting in overdose of the Efudex cream product. In all four of these cases the patients either misunderstood or disregarded the physician's instructions. Outcomes included severe skin irritation and bacterial infection. One of the six cases involves the wrong route of administration of the Efudex solution. The patient inadvertently applied the solution in the eye instead of on the skin. The patient experienced a burning sensation and was instructed to flush the eye with water. There was no adverse outcome. The remaining case involves dispensing of the wrong drug (Eurax for Efudex).

3.1.5 Safety evaluator risk assessment

The primary Safety Evaluator, affording careful evaluation to drug names beginning with the letters 'T','F', and 'L', conducted independent searches which identified an additional six names with similarity to Tolak. The names identified to have look-alike similarities are: Flolan, Folicet, and Totect. The names identified to have sound-alike similarity are (b) (4)***, (b) (4)***, and Tolak angin. As such, a total of thirty names were analyzed to determine if the drug names could be confused with Tolak and if the drug name confusion would likely result in a medication error.

All of the identified names were determined to have some orthographic and/or phonetic similarity to Tolak, and thus determined to present some risk for confusion. Failure modes and effects analysis (FMEA) was then applied to determine if the proposed name, Tolak, could potentially be confused with any of the thirty names and lead to medication error.

This analysis determined that the name similarity between Tolak and the identified names was unlikely to result in medication errors for all thirty products. Nine names (Zoloft, Tolcapone, Folicet, Tolectin, Penlac, Tiazac, Tolerex, Folic Acid, and Cholac) were not considered further because they lack convincing orthographic and/or phonetic similarities with Tolak. Two names (Toilax and Tolak angin) are used for products marketed in foreign countries, and thus determined by FMEA to pose minimal risk for error in the usual practice setting (Appendix C). Two names ((b) (4)*** and (b) (4)***) are proposed proprietary names for other products within the Agency which have not been approved or were approved under a different proprietary name, and thus were determined by FMEA to pose a minimal risk of error in the usual practice setting (Appendix D). (b) (4)***was the first name submitted by the applicant for the product under review. DDMAC found the name unacceptable and the review division concurred and thus the name was not reviewed (see OSE review 2007-2285). Tubex is the trade name of a line of pre-filled glass cartride syringes. The different context of use decreases the risk of confusion with a drug product such as Tolak. One name (Tolaz) could not be found in commonly used drug references such as Clinical Pharmacology Online, Facts & Comparisons, Micromedex, STATRef, the Orange Book, or the Red Book and thus determined by FMEA to pose minimal risk for error in the usual practice setting. Tolax is a chemical substance which acts as a muscle relaxant. No further information is available.

For seven names (Flolan, Tylox, Teslac, Terak, Lobac, Taxol, and Folex) it was determined that medication errors were unlikely because the products do not overlap in strength or dosage with Tolak and have limited orthographic and/or phonetic similarity to Tolak (see Appendix E).

The remaining six names (Foltx, Colax, Tarka, Talc, Totect, and Folate) had some numerical overlap with Tolak in dosage and strength, but analysis of the failure modes did not determine the effect of this similarity to result in medication errors in the usual practice setting (see Appendix F).

3.2 LABEL AND LABELING RISK ASSESSMENT

Review of the container labels and carton labeling identified several areas of vulnerability that could lead to medication error, specifically with respect to clear communication of the product name, strength, and net quantity.

3.2.1 All Labels and Labeling

The 'Rx only' statement is missing.

The established name is stated inconsistently throughout the labels and labeling as fluorouracil, 5-fluorouracil, or 5-FU.

3.2.2 Container Label and Carton Labeling

The proprietary name is presented within a graphic.

Although the container labels and carton labeling have the name (b) (4) on them, the applicant plans to utilize tallman lettering 'AK' for the last two letters in TolAK.

The established name appears on the right side of the principal display panel, away from the proprietary name.

The strength is presented in front of the established name.

The net quantity statement appears directly above the strength and has greater prominence.

On the container label, the route of administration is presented in light blue font on a white background, which is difficult to read.

On the carton labeling, the established name, strength, dosage form, and net quantity are presented in dark blue font on a blue background, which is difficult to read.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

The results of the Proprietary Name Risk Assessment found that the proposed name, Tolak, has some similarity to thirty other proprietary drug names, but the findings of the FMEA process indicate that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors.

The findings of the Proprietary Name Risk Assessment are based upon current understanding of factors that contribute to medication errors involving name confusion. Although we believe the findings of the Risk Assessment to be robust, our findings do have limitations. First, because our assessment involves a limited number of practitioners, it is possible that the analysis did not identify a potentially confusing name. Also, there is some possibility that our Risk Assessment failed to consider a circumstance in which confusion could arise. However, we believe that these limitations are sufficiently minimized by the use of an Expert Panel and the Prescription Studies that involved 123 FDA practitioners.

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics, future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit

our findings. To help counterbalance this impact, we recommend that the proprietary name be re-submitted for review if approval of the product is delayed beyond 90 days.

4.2 LABEL AND LABELING RISK ASSESSMENT

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed carton and container labels are vulnerable to confusion that could lead to medication errors. We note needed improvements with respect to the prominence, presentation, and consistency of information on the container label and carton labeling.

Specifically, the proprietary and established names and strength are presented in an unconventional format, which makes it difficult for the reader to locate this important information. First, the proprietary name is surrounded by a graphic, which provides no meaningful information to patients or healthcare practitioners. Because of this graphic, the established name appears on the right side of the principal display panel, away from the proprietary name and in this position lacks prominence. The established name is also inconsistently presented throughout the labels and labeling (i.e., fluorouracil, 5-fluorouracil or (b) (4)). Additionally, the dosage form is not presented immediately following the established name but instead appears above the established name. Moreover, the dosage form includes the word topical, which is duplicative because it is already stated beneath the proprietary name. Finally the strength is presented before the established name. The proprietary name, established name (including the dosage form) and strength are the most important information on the principal display of the labels and labeling. Presenting this information in this unusual manner increases the opportunity for confusion. Practitioners are accustomed to seeing the proprietary name, established name and dosage form, followed by the strength when looking at a drug label/labeling. This preferred placement allows for easy identification by a healthcare practitioner and decreases confusion.

Additionally, the applicant has informed the review division that they plan to use capital letters for the ending of the proprietary name (i.e., TolAK). This presentation gives more prominence to one portion of the name and distorts the readability. We learned that this is intended to highlight the indication of use, Actinic Keratosis. However, the use of tallman lettering should be used conservatively to mitigate wrong drug errors and not to highlight the indication of use. Revising the letters to lower case 'ak' will provide consistency and clarity to the appearance of the proprietary name.

The applicant has chosen to present information on the container label and carton labeling in a dark blue colored font against a (b) (4) background. Similarly, some information is presented in (b) (4) blue colored font against a white background. Overall, these colors do not provide sufficient contrast, which decreases the readability of the container labels and carton labeling.

Additionally, we note that the net quantity statement appears very close to the product strength and has the same prominence. This may be confusing because there is numerical overlap between the strength and net quantity (4% vs. 40 grams). Finally, the "Rx only" statement has been omitted from the container label and carton labeling. This is not in accordance with Section 503(b)(4)(A) of the Federal Food Drug and Cosmetic Act.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Tolak, does not appear to be vulnerable to name confusion that could lead to medication errors. As such, the Division of Medication Error Prevention does not object to the use of the proprietary name, Tolak, for this product at this time.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. The Division of Medication Error Prevention believes the risks we have identified can be addressed and mitigated prior to drug approval.

5.1 COMMENTS TO THE DIVISION

1. The Division of Medication Error Prevention does not object to the use of the proprietary name Tolak for this product at this time. However, if **any** of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review. If the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.
2. The Division of Medication Error Prevention believes the Label and Labeling risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the applicant with regard to this review. If you have further questions or need clarifications, please contact Janet Anderson, project manager, at 301-796-0675.

5.2 COMMENTS TO THE APPLICANT

5.2.1 Proprietary Name

1. The Division of Medication Error Prevention does not object to the use of the proprietary name Tolak for this product at this time.
2. If **any** of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review. This name will be re-evaluated 90 days prior to approval.

5.2.2 Labels and Labeling

A. All Labels and Labeling

1. The proprietary and established names and the strength should be presented in the following format on all of the labels and labeling:

   Tolak
   (Fluorouracil) Cream 4%

2. Revise the font lettering in the proprietary name, Tolak, so that the final letters ‘AK’ appear in lower case, to provide consistency and clarity to the appearance of the drug name.

3. Add the “Rx only” statement to the principal display panel.

4. Ensure that the established name is consistently listed as “fluorouracil” throughout all product labeling.

B. Container Label and Carton Labeling

1. Increase the prominence of the established name so that it is at least ½ the size of the proprietary name according to 21 CFR 201.10(g)(2).

2. Remove the graphic surrounding the proprietary name.

3. Move the net quantity statement “40 g” away from the strength and present it with less prominence.

4. On the container label, replace the (b) (4) blue font with a contrasting color against the white background.

5. On the carton labeling, replace the dark blue font with a contrasting color against the (b) (4) background.

6 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. Micromedex Integrated Index (http://weblern/)

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

3. Phonetic and Orthographic Computer Analysis (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for the Division of Medication Error Prevention, FDA.

4. Drug Facts and Comparisons, online version, St. Louis, MO (http://weblern/)

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

5. AMF Decision Support System [DSS]

DSS is a government database used to track individual submissions and assignments in review divisions.

6. Division of Medication Errors and Technical Support proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention from the Access database/tracking system.

7. Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, discontinued drugs and "Chemical Type 6" approvals.

8. Electronic online version of the FDA Orange Book (http://www.fda.gov/cder/ob/default.htm)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

9. United States Patent and Trademark Office http://www.uspto.gov.

Provides information regarding patent and trademarks.

10. Clinical Pharmacology Online (http://weblern/)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

11. Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. Natural Medicines Comprehensive Databases (http://weblern/)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

13. Stat!Ref (http://weblern/)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

14. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

List contains all the recognized USAN stems.

15. Red Book Pharmacy's Fundamental Reference

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

16. Lexi-Comp (www.pharmacist.com)

A web-based searchable version of the Drug Information Handbook.

17. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. We also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The Medication Error Staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, we will consider the Sponsor's intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, we also consider a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstokes Downstrokes Cross-stokes	• Names may look similar when scripted, and lead to drug name confusion in written communication

		Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B:

Tolak CDER Prescription Study Responses

Outpatient Prescription	Voice Prescription	Inpatient Medication Order
Tolack	Tolac	Folah
Tolak	Tolac	Folah
Tolak	tolac	Folah
Tolak		Folah
Tolak		Folah
Tolak		Folak
Tolak		Talah (Falah)
Tolak		Tolah
Tolak		Tolah
Tolak		Tolah
Tolak		Tolah
Tolak		Tolar
Tolak		
Tolak		

Appendix C: Proprietary names used only in Foreign Countries

Proprietary Name	Similarity to Tolak	Country
Toilax	Look and Sound	Bisacodyl available in Denmark, Finland, Ireland, Norway, Sweden, and the Netherlands
Tolak angin	Look and Sound	Unspecified herbs for medicinal use available in Australia

Appendix D: Proposed proprietary names for products not approved or approved with another name

Proprietary Name	Similarity to Tolak
(b) (4) ***	Look and Sound
(b) (4) ***	Look and Sound

Appendix E: Products with no numerical overlap in strength and dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Tolak **(Fluorouracil) Cream**		**4%**	**Apply once daily in an amount sufficient to cover the lesions with a thin film. Apply for a period of 4 weeks as tolerated.**
Flolan (epoprostenol)	Look	Injection: 0.5 mg/17 mL vial and 1.5 mg/17 mL vial	2 ng/kg/min continuous intravenous infusion
Tylox (acetaminophen/oxycodone)	Look and Sound	Capsules: acetaminophen 500 mg/oxycodone 5 mg	1 to 2 capsules orally every 6 hours as needed
Teslac (testolactone)	Look and Sound	Tablets: 50 mg	250 mg orally four times daily
Terak (oxytetracycline/polymyxin B sulfate)	Look and Sound	Ophthalmic ointment: 10,000 units/g polymyxin B sulfate and 5 mg/g oxytetracycline HCl	Apply ½ inch of ointment on lower lid of affected eye(s) 2 to 4 times daily
Lobac (salicylamide/ phenyltoloxamine/ acetaminophen)	Look	Capsules: 200 mg salicylamide 20 mg penyltoloxamine 300 mg acetaminophen	2 capsules by mouth four times daily
Taxol (paclitaxel)	Look	Injection: 6 mg/mL (30 mg/5 mL multi-dose vial; 100 mg/16.7 mL multi-dose vial, 300 mg/50 mL multi-dose vial)	175 mg/m^2 intravenously over 3 hours every 3 weeks
Folex (methotrexate) *Discontinued; generic formulations available	Look and Sound	Injection: 25 mg/vial; 50 mg/vial; 100 mg/vial; 250 mg/vial	20 to 60 mg/m^2 intravenously every 28 days

Appendix F: Potential confusing name with numerical overlap in strength or dose

Failure Mode: Name confusion	**Causes (could be multiple)**	**Effects**
Tolak (Fluorouracil) Cream	**4%**	**Usual dose: Apply once daily in an amount sufficient to cover the lesions with a thin film. Apply for a period of 4 weeks as tolerated.**
Folate (folic acid) Tablets: 0.4 mg, 0.8 mg (OTC); 1 mg (Rx) Injection: 5 mg/mL	Orthographic similarity ('Tola' vs 'Fola') Numerically similar strengths (4% vs. 0.4 mg) Overlapping frequency (once daily)	Differing product characteristics minimize the likelihood of medication errors in the usual practice settings. *Rationale:* The risk of medication errors is reduced by the differing product characteristics. Tolak and Folate differ in dosage form (cream vs. tablet or injection); dose (sufficient amount vs. 0.4 to 1 mg); route of administration (topical vs. oral or subcutaneous/intramuscular injection); and prescriber population (dermatologist vs. general practitioner or hematologist).
Colax (bisacodyl tablets) 5 mg *Discontinued; generic versions available	Overlapping frequency (once daily)	Differing product characteristics minimize the likelihood of medication errors in the usual practice settings. *Rationale:* The risk of medication errors is reduced by the differing product characteristics. Tolak and Colax differ in dosage form (cream vs. tablet); dose (sufficient amount vs. 10 to 15 mg); route of administration (topical vs. oral); prescriber population (dermatologist vs. general practitioner or gastroenterologist); and prescription status (prescription vs. over-the-counter). Also, Colax may be ordered by the names bisacodyl or Dulcolax.
Tarka (trandolapril immediate release/verapamil extended release tablets) 2 mg/180 mg 4 mg/240 mg 1 mg/240 mg 2 mg/240 mg	Overlapping strength (4% vs. 4 mg/240 mg) and frequency (once daily)	Orthographic differences as well as differing product characteristics minimize the likelihood of medication errors in the usual practice settings. *Rationale:* The risk of medication errors is reduced by orthographic differences in the names as well as differing product characteristics. Although the names contain some of the same letters ('T', 'a', and 'k') they are not in the same order. Also, the 3 upstrokes in Tolak help to distinguish it

		from Tarka, which has 2 upstrokes. Tolak and Tarka differ in dosage form (cream vs. tablet); dose (sufficient amount vs. 1 mg to 4 mg trandolapril component and 120 mg to 480 mg verapamil component); route of administration (topical vs. oral); and prescriber population (dermatologist vs. general practitioner or cardiologist).
Talc (Powder: 5 grams Aerosol: 4 grams)	Overlapping strength (4% vs. 4 grams)	Orthographic differences as well as differing product characteristics minimize the likelihood of medication errors in the usual practice settings. *Rationale:* The risk of medication errors is reduced by orthographic differences in the names as well as differing product characteristics. Although the names have similar beginnings ('Tol' vs. Tal') the endings serve as a differentiator ('ak' vs. 'c'). Also, Talc appears shorter than Tolak. Tolak and Talc differ in dosage form (cream vs. powder or aerosol); dose (sufficient amount vs. 5 grams of powder dissolved in 50 to 100 mL Sodium Chloride Injection or 4 to 8 grams of aerosol); route of administration (topical vs. intrapleural); length of treatment (4 weeks vs. one time); prescriber population (dermatologist vs. pulmonologist or intensivist); and setting of use (outpatient vs. inpatient).
Totect (dexrazoxane injection 500 mg/vial)	Overlapping frequency (once daily)	Orthographic differences as well as differing product characteristics minimize the likelihood of medication errors in the usual practice settings. *Rationale:* The risk of medication errors is reduced by orthographic differences in the names as well as differing product characteristics. Although the names have similar beginnings ('Tol' vs. Tot') the endings serve as a differentiator ('ak' vs. 'ect'). Tolak and Totect differ in dosage form (cream vs. injection); dose (sufficient amount vs. 1000 mg/m^2 for days 1 and 2; 500 mg/m^2 day 3); route of administration (topical vs. intravenous); length of treatment (4 weeks vs. 3 days); prescriber population (dermatologist vs. oncologist); and setting of use (outpatient vs. inpatient or clinic).

Foltx (folic acid 2.5 mg/ cyanocobalamin 2 mg/ pyridoxine 25 mg tablet)	Overlapping frequency (once daily)	Orthographic differences as well as differing product characteristics minimize the likelihood of medication errors in the usual practice settings. *Rationale:* The risk of medication errors is reduced by orthographic differences in the names as well as differing product characteristics. Although the names have a similar beginning ('Tol' vs. 'Fol') the endings serve as a differentiator ('ak' vs. 'tx'). Tolak and Foltx differ in dosage form (cream vs. tablet); dose (sufficient amount vs. 1 to 2 tablets); route of administration (topical vs. oral); and prescriber population (dermatologist vs. general practitioner or hematologist).

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 11, 2007
To:	Susan Walker, MD, Director Division of Dermatology and Dental Products
Thru:	Linda Y. Kim-Jung, PharmD, Team Leader Denise P. Toyer, PharmD, Deputy Director Carol A. Holquist, RPh, Director Division of Medication Errors and Technical Support
From:	Tara Turner, PharmD, Safety Evaluator Division of Medication Errors and Technical Support
Subject:	Proprietary Name Review
Drug Name(s):	(b) (4) (5-fluorouracil) Cream 4%
Application Type/Number:	NDA 22-259
Applicant/sponsor:	Hill Dermaceuticals, Inc.
OSE RCM #:	2007-2285

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