CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-334

PROPRIETARY NAME REVIEW(S)

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:	March 10, 2009
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Thru:	Melina Griffis, R.Ph, Acting Team Leader Denise Toyer, PharmD., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Anne Crandall, PharmD., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name, Label and Labeling Review
Drug Name(s):	Afinitor (Everolimus) Tablets 5 mg and 10 mg
Application Type/Number:	NDA: 22-334
Applicant:	Novartis Pharmaceuticals
OSE RCM #:	2009-264

*** **Note: This review 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, Afinitor, is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Afinitor, for this product. This is considered a final review, however, if approval is delayed beyond 90 days from the date of this review, the proprietary name should be resubmitted for re-review.

Additionally, the Applicant provided revised labeling based on DMEPA recommendations (OSE review # 2008-1236)). DMEPA finds the revised labels to be adequate.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Drug Oncology Products for an assessment of the proposed proprietary name, Afinitor, regarding potential name confusion with other proprietary or established drug names in the usual practice setting. The proposed proprietary name, Afinitor, was previously reviewed by DMEPA in 2008 (OSE Consult # 2008-257) without objection. Container labels, carton and insert labeling were also provided to be evaluated from a medications errors perspective. DMEPA reviewed the label and labeling in conjunction with the proprietary name review

1.2 PRODUCT INFORMATION

Afinitor (Everolimus) has been in clinical development as an investigational immunosuppressant drug and for the treatment of advanced renal cell carcinoma. An NDA ——— for the prophylaxis of organ rejection in cardiac transplantation was submitted and the Agency has issued approvable letters on October 20, 2003 and August 27, 2004 and did not object to the trade name Certican proposed for this product and indication. However, approval of this indication has been delayed and is likely to go beyond 2008. Therefore, the sponsor has requested the review of the proposed proprietary name, Afinitor, for the NDA submission (dated June 30, 2008) for the treatment of advanced renal cell carcinoma. The upcoming PDUFA date for this application is March 30, 2009,

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2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis conducting a Proprietary Name Risk Assessment and Label and Labeling Risk Assessment. The primary focus of the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis 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. [1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

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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.

For the proprietary name, Afinitor, the DMEPA staff 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). The Division of Medication Error Prevention also conducts 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). In this case, an internal CDER prescription analysis study was conducted in OSE Review #: 04-0018, and was therefore not repeated for this review.

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 Mode 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. The Division of Medication Error Prevention and Analysis uses 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 DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed name 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, DMEPA staff considers 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]

2.1.1 Search Criteria

The DMEPA Staff considers 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 'A' 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.[45]

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

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

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

To identify drug names that may look similar to Afinitor, DMEPA also considers the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (eight letters), upstrokes (three, capital letter 'A', lower case 'f' and 't'), downstrokes (lower case 'f'), cross-strokes ('t'), and dotted letters (two). Additionally, several letters in Afinitor may be vulnerable to ambiguity when scripted, including the letter uppercase 'A' may appear as 'C'; lower case 'i' may appear as a lower case 'e' or 'o'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Afinitor.

When searching to identify potential names that may sound similar to Afinitor, the DMEPA staff search for names with similar number of syllables (four), stresses (A-FIN-i-TOR or AH-fin-i-TOR), and placement of vowel and consonant sounds. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

DMEPA also considers 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, DMEPA was provided with the following information about the proposed product: the proposed proprietary name (Afinitor), the established name (Everolimus), proposed indication (advanced renal cell carcinoma), strength (5 mg and 10 mg), dose (1 tablet), frequency of administration (once daily), route (oral) and dosage form of the product (tablet). Appendix A provides a more detailed listing of the product characteristics the DMEPA staff generally takes into consideration.

Lastly, the DMEPA staff also considers 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 DMEPA staff provides 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, Afinitor, was provided to the DMEPA 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 Afinitor using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the DMEPA 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 DMEPA staff review the United States Adopted Names (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 by DMEPA to gather CDER professional opinions on the safety of the product and the proprietary name, Afinitor. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of the Division of

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

Medication Error Prevention and Analysis (DMEPA) 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 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the primary Safety Evaluator 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, the Division of Medication Error Prevention and Analysis seeks 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.

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 Afinitor convincing 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 Afinitor 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 possess 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

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

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.

DMEPA 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. DMEPA identifies 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. DMEPA identifies 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 name and another drug product.

In the event that DMEPA objects 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 the use of the name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then DMEPA 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 Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the Institute of Medicine, the World Health Organization, the Joint Commission on Accreditation of Healthcare Organizations, and the Institute of Safe Medication Practices, 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, DMEPA contends 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 Applicant, 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 Applicants 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, DMEPA believes 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 DMEPA objects 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. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA 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 DMEPA may be able to provide the Applicant 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, dosage 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] to identify potential errors with all medications similarly packaged, labeled or prescribed. The Division uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

On January 12, 2009 the Applicant submitted the following labels for our review:

- Blister Card Container Labels: (Appendix G)
- Carton Labeling: (Appendix H)
- Package Insert Labeling (no image)

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

The searches yielded a total number of 17 names as having some similarity to the name Afinitor.

Thirteen names were thought to look like Afinitor, which include: Claritin, Definity, Lipitor, Carnitor, Clinitek, Atenetic, Atenolol, Criniton, Zaditor, [redacted] Afifon. The remaining four names, Alfenta, [redacted] were thought to look and sound similar to Afinitor. b(4)

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

Additionally, the Division of Medication Error Prevention and Analysis did not identify any United States Adopted Names (USAN) stems in the name Afinitor, as of the last date searched on February 24, 2009.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by DMEPA staff (see section 3.1.1. above) and noted no additional names thought to have orthographic or phonetic similarity to Afinitor.

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 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator resulted in no additional names which were thought to look or sound similar to Afinitor and represent a potential source of drug name confusion.

Five (Lipitor, Carnitor, Zaditor, Alfenta, and [redacted] f the 17 names identified in the database searches were previously reviewed in the initial Afinitor proprietary name review (OSE # 2008-1234). Afinitor has not undergone any product characteristic changes since the previous review therefore these names did not undergo further analysis in this review.

Additionally, we note that attempts to identify the drug names [redacted] ere unsuccessful. We assume that the name was misspelled during the search process (i.e. [redacted] for [redacted]. Thus, we evaluated [redacted] (identified by the primary safety evaluator). b(4)

One name, [redacted] was determined to lack orthographic similarity to Afinitor, therefore was not analyzed further.

Eleven names were analyzed to determine if drug names could be confused with Afinitor and if the drug name confusion could likely result in a medication error.

Failure mode and effect analysis (FMEA) was then applied to determine if the proposed name could potentially be confused with any of the 11 names and lead to medication errors. This analysis determined that the name similarity between Afinitor and the identified names was unlikely to result in medication errors with any of the 11 products identified for the reason presented in Appendices C through F.

3.2 LABEL AND LABELING

All previous recommendations from OSE review # 2008-1236 have been implemented.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

Twelve names were evaluated for their potential similarity to the proposed name, Afinitor. The FMEA indicates that the proposed name is not likely to result in name confusion that could lead to medication errors.

4.2 LABEL AND LABELING RISK ASSESSMENT

All label and labeling recommendations have been implemented, therefore we have no comments at this time.

5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Afinitor, is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication

Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Afinitor, for this product at this time. Additionally, DDMAC does not object to the proposed name, Afinitor from a promotional perspective.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. If the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

All label and labeling recommendations were sufficiently implemented in the revised label and labeling which was submitted January 12, 2009. Therefore, DMEPA currently has no further comments regarding the Afinitor label and labeling.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

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 Sandra Griffith, at 301-796-2445.

6.2 COMMENTS TO THE APPLICANT

6.2.1 Proprietary Name

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

This is considered a final review, however, if approval is delayed beyond 90 days from the date of this review, the proprietary name should be resubmitted for re-review.

If <u>any</u> of the proposed product characteristics are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

6.2.2 Label and Labeling Review

All recommendations from the Afinitor Label and Labeling review (OSE review # 2008-1236) have been implemented satisfactorily. There are no further comments or recommendations at the present time.

7 REFERENCES

1. ***OSE reviews 2008-1236 and 2008-257.*** *December 8, 2008 and April 11, 2008 respectively.*

2. ***Micromedex Integrated Index*** *(http://csi.micromedex.com)*

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

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

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. 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 and Analysis, FDA.

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

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 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.

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, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and 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. ***U.S. Patent and Trademark Office*** *(http://www.uspto.gov)*

Provides information regarding patent and trademarks.

10. ***Clinical Pharmacology Online*** *(www.clinicalpharmacology-ip.com)*

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 trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. ***Natural Medicines Comprehensive Databases*** *(www.naturaldatabase.com)*

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

13. ***Stat!Ref*** *(www.statref.com)*

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.lexi.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. The Division of Medication Error Prevention and Analysis 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 (i.e. "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, the Division of Medication Error Prevention will consider the Applicant's intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, the Division of Medication Error Prevention and Analysis also considers 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 Upstrokes Downstrokes	• Names may look similar when scripted, and lead to drug name confusion in written communication

		Cross-strokes 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: Proprietary names with no orthographic similarity to Afinitor

Proprietary Name	Source
[redacted]	EPD

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

Appendix C: Name is not a drug and will not be confused with Afinitor in the usual practice setting

Afinitor	Similarity	Oral tablet
Clinitek	Look-alike	Strips for urine chemistry

Appendix D: Foreign proprietary names with similar orthographic characteristics with Afinitor

Proprietary Name (established name)	Country	Similarity to Afinitor
Atenetic (Atenolol/Chlorthalidone)	Ireland	Look-alike
Criniton (Thymol, Salicylic acid, rosemary oil)	Germany	Look-alike
Afifon (Beclomethasone)	Israel	Look-alike

Appendix E: Proprietary name cannot be found in any commonly used drug references

Proprietary Name	Source/Website	Owner
[redacted]	EPD/USPTO	Novartis
[redacted]	EPD/USPTO	Novartis
[redacted]	EPD/USPTO	Novartis
[redacted]	EPD/USPTO	Novartis

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Appendix F: Proprietary names for prescription drugs with orthographic similarity to Afinitor with numerical overlap in dose and/or strength

Afinitor **(Everolimus)**	**5 mg and 10 mg oral tablet**	**Usual adult dose: 5 mg or 10 mg orally once daily**
Failure Mode: **Orthographic name confusion and overlapping product characteristics**	**Causes (could be multiple)**	**Effect**
Claritin (Loratadine) 10 mg oral capsule, tablet 1 mg/mL oral syrup 10 mg by mouth once daily	Orthographic ('A' resembles 'C' when scripted, 2 dotted letters, 'i' in both Afinitor and Claritin, cross-stroke, 't' near end of both names, both are eight letters)	Orthographic differences minimize the likelihood of medication errors. Rationale: the 'f' in Afinitor provides a cross-stroke and in addition may provide a down-stroke (depending on how it is scripted) vs. an 'l' in Claritin which has no cross-stroke or down-stroke, the dotted 'i's in Afinitor occur at the third letter and the fifth letter vs. the fifth and seventh in Claritin. Claritin has a dotted letter-cross stroke-dotted letter 'iti' vs. dotted letter-cross strike followed by an 'o' 'ito'. Claritin now is only available as an Over-the-Counter (OTC) medication and no longer available as an Rx product, therefore Claritin most likely will not be written on a prescription form.
Atenolol 25 mg, 50 mg and 100 mg oral tablet, 5 mg/10 mL solution of injection 25 mg to 200 mg by mouth once daily, 5 mg intravenously over 5 minutes, may be followed with another 5 mg based on response.	Orthographic (both begin with 'A', both have up-stroke for second letter; 'f' in Afinitor and 't' in Atenolol, 'inito' resembles 'enolo' when scripted)	Orthographic differences minimize the likelihood of medication errors. Rationale: Afinitor contains 2 dotted 'i's vs. no dotted letters in Atenolol, Afinitor contains an 'A', 'f' and 't' which provides three cross strokes vs. Atenolol which contains 'A' and 't' which only provides two cross-strokes. Atenolol has four upstrokes and ends with 'l' which provides an upstroke at the end unlike Afinitor.

Afinitor **(Everolimus)**	**5 mg and 10 mg oral tablet**	**Usual adult dose: 5 mg or 10 mg orally once daily**
Failure Mode: **Orthographic name confusion and overlapping product characteristics**	**Causes (could be multiple)**	**Effect**
Definity (Perflutren) 6.52 mg/mL, 2 mL vial for injection, as a bolus dose or infusion [redacted] [redacted]	Orthographic (Both have 2 dotted 'i's and three upstrokes, both are eight letters in length)	Orthographic and product characteristic differences minimize the likelihood of medication errors Afinitor is an oral medication vs. Definity which is an injection. Afinitor is taken once daily, chronically to [redacted] vs. Definity is used for a one time procedure for imaging to opacify the left ventricular chamber as a one time order. The maximum dose for Definity is either two bolus doses (one dose followed ½ hour later bay another dose) or one infusion with the doses reported in either microliters or milliliters. The maximum dose for Afinitor is 5 mg or 10 mg once daily. Definity would only be given in the hospital or wherever imaging is available as the patient must begin imaging immediately after injection.

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6 Page(s) Withheld

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