

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202714Orig1s000

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
Office of Medication Error Prevention and Risk Management**

Proprietary Name Review--Final

Date: June 21, 2012

Reviewer: Sarah K. Vee, PharmD, Safety Evaluator
Division of Medication Prevention and Analysis

Team Leader Yelena Maslov, PharmD, Acting Team Leader
Division of Medication Prevention and Analysis

Drug Name and Strength: Kyprolis (Carfilzomib) for Injection
60 mg per vial

Application Type/Number: NDA 202714

Applicant/sponsor: Onyx Pharmaceuticals, Inc.

OSE RCM #: 2012-1134

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

CONTENTS

1	INTRODUCTION	3
2	METHODS AND DISCUSSION	3
3	CONCLUSIONS.....	3
3.1	Comments to the Applicant.....	3
4	REFERENCES	4
	Appendices.....	5

1 INTRODUCTION

This re-assessment of the proposed proprietary name, Kyprolis, is written in response to the anticipated approval of this NDA within 90 days from the date of this review. DMEPA found the proposed name, Kyprolis, acceptable in OSE Review 2011-3706, dated December 8, 2011.

2 METHODS AND DISCUSSION

For re-assessments of proposed proprietary names, DMEPA searches a standard set of databases and information sources (see section 4) to identify names with orthographic and phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name review. For this review we used the same search criteria described in OSE Review 2011-3706. We note that none of the proposed product characteristics were altered. However, we evaluated the previously identified names of concern considering lessons learned from recent post-marketing experience related to proprietary name confusion, which has not altered our previous conclusion regarding the acceptability of the proposed proprietary name, Kyprolis.

The searches of the databases yielded two new names (Rezulin and Ryzodeg^{***}), thought to look similar to Kyprolis and represent a potential source of drug name confusion. Failure mode and effects analysis was applied to determine if the proposed proprietary name could potentially be confused with Ryzodeg^{***} and lead to medication errors. This analysis determined that the name similarity between Kyprolis and Ryzodeg^{***} was unlikely to result in medication error for the reasons presented in Appendix B.

Additionally, DMEPA searched the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. The Safety Evaluator did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of June 21, 2012. The Office of Prescription Drug Promotion (OPDP) re-reviewed the proposed name on May 17, 2012 and had no concerns regarding the proposed name from a promotional perspective.

3 CONCLUSIONS

The re-evaluation of the proposed proprietary name, Kyprolis, did not identify any vulnerabilities that would result in medication errors with any additional names noted in this review. Thus, DMEPA has no objection to the proprietary name, Kyprolis, for this product at this time.

DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Hematology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

If you have further questions or need clarifications, please contact Sue Kang, OSE project manager, at 301-796-4216.

3.1 COMMENTS TO THE APPLICANT

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

^{***} This document contains proprietary information that should not be released to the public

REFERENCES

1. **OSE Review 2011-3706 Kyprolis (carfilzomib) Name Review [acceptable], December 8, 2011, Kimberly DeFronzo.**
2. ***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.
3. ***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.
4. ***Division of Medication Error Prevention and Analysis Proprietary Name Consultation Request***
Compiled list of proposed proprietary names submitted to the Division of Medication Error Prevention and Analysis for review. The list is generated on a weekly basis from the Access database/tracking system.

Appendix A: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

Proprietary Name	Active Ingredient	Similarity to Kyprolis	Failure Preventions
Rezulin	Troglitazone	Orthographic	NDA 20720 Withdrawn FR Effective 1/10/2003

Appendix B: FMEA Table

Proposed Name: Kyprolis (Carfilzomib) Strength and Dosage Form: 60 mg/vial powder for injection Usual Dose: 20 mg/m ² for the first treatment cycle (28 days) and 27 mg/m ² for all subsequent cycles intravenously twice weekly on consecutive days.	Cause of Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	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
Ryzodeg ^{***} (insulin degludec and insulin aspart)		

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH K VEE
06/22/2012

YELENA L MASLOV
06/22/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name Review

Date: December 8, 2011

Reviewer: Kimberly DeFronzo, RPh, MS, MBA
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength(s): Kyprolis (Carfilzomib) for Injection
60 mg per vial

Application Type/Number: NDA 202714

Applicant/Sponsor: Onyx Pharmaceuticals, Inc.

OSE RCM #: 2011-3706

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

CONTENTS

1	INTRODUCTION	1
1.1	Product Information.....	1
2	RESULTS	1
2.1	Promotional Assessment.....	1
2.2	Safety Assessment	1
3	CONCLUSIONS.....	5
3.1	Comments to the Applicant	5
4	REFERENCES.....	6
	APPENDICES	9

1 INTRODUCTION

This review evaluates the proposed proprietary name, Kyprolis, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A, respectively.

1.1 PRODUCT INFORMATION

The following product information is provided in the September 27, 2011, proprietary name submission.

- Established Name: Carfilzomib
- Indication of Use: Relapsed and refractory multiple myeloma
- Route of administration: Intravenous
- Dosage form: Lyophilized powder for injection
- Dose: 20 mg/m² for the first treatment cycle (28 days) and 27 mg/m² for all subsequent cycles twice weekly on consecutive days for 3 weeks (Days 1, 2, 8, 9, 15, 16 of 28-day cycle), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered 1 treatment cycle.
- How Supplied: Cartons containing one vial of 60 mg per vial (2 mg/mL after reconstitution)
- Storage: Unopened vials should be stored refrigerated (2°C to 8°C; 36°F to 46°F)
- Container and Closure systems: Drug product is supplied in a single-use (b) (4) vial (b) (4) containing a deliverable dose of 60 mg of Carfilzomib as a white to off-white lyophilized cake or powder. Each vial is individually packed with the package insert in a carton chipboard box.

2 RESULTS

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

2.1 PROMOTIONAL ASSESSMENT

OPDP determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Hematology Products concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

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

2.2.1 *United States Adopted Names (USAN) SEARCH*

On October 13, 2011, the United States Adopted Name (USAN) stem search identified that a USAN stem is not present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

This proprietary name comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that is misleading or can contribute to medication error.

2.2.3 FDA Name Simulation Studies

Thirty eight practitioners participated in DMEPA's prescription studies (n=16 in the "Inpatient" group, n=12 in the "Outpatient" group, and n=10 in the "Voice" or verbal group). Approximately two-thirds of the participants correctly identified the proposed name as Kyprolis (n=24). The remainder of the group misinterpreted the proposed name Kyprolis with variations in the spelling. None of the 38 participants indicated confusion with any currently marketed product.

See Appendix C for the complete listing of interpretations from the FDA verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines

In response to the OSE October 17, 2011, e-mail, the Division of Hematology Products (DHP) did not forward any comments or concerns relating to the proposed name at the initial phase of the proprietary name review.

2.2.5 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Kyprolis. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Kyprolis identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines. Table 1 also includes the names identified from the FDA Prescription Simulation or by Drug Safety Institute, Inc. (DSI) not previously identified by DMEPA. These names will be included in the analysis.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines, FDA Name Simulation Studies, and External Name Study if applicable)

Look Similar		Sound Similar		Look & Sound Similar	
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
Bystolic	FDA	Captopril	FDA	Kapidex	FDA
Hypaque Sodium	FDA	Ketorolac	External	Kineret	External
Hyperal	FDA			Kytril	FDA & External
HyperHep B	FDA				
Hyper-Sal	FDA				
Hypertears	FDA				
Hypertensa	FDA				
Hypertonic Saline	FDA				
Hyphanox	FDA				
Keppra	FDA & External				
Kybernin P	FDA				
Kynapid***	FDA				
(b) (4)	FDA				
Kytil	FDA				
Reyataz	FDA				
Risperdal	FDA				
Ryzolt	FDA				
Victrelis	FDA				
Caprelsa	FDA				
Cabergoline	External				
Cialis	External				
Keralyt	External				
Kyolic	External				
Nitrodisc	External				

Look Similar		Sound Similar		Look & Sound Similar	
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
Onsolis	External				
Tacrolimus	External				
Zyprexa	External				
Kabolin	External				
Kapectolin	External				
Keralac	External				
Kerlix	External				
Kerodex	External				
Kerol	External				
Key-Plex	External				
Key-Pred	External				
Kinerase	External				
Kutrase	External				
K-Y Plus	External				

Our analysis of the 43 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined all 43 names will not pose a risk for confusion as described in Appendix D through E.

2.2.6 Communication of DMEPA's Final Decision to Other Disciplines

DMEPA communicated our findings to the Division of Hematology Products (DHP) via e-mail on December 5, 2011. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Hematology Products on December 8, 2011, they stated no concern with the proposed proprietary name, Kyprolis.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective.

If you have further questions or need clarifications, please contact Sue Kang, OSE Project Manager, at 301-796-4216.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Kyprolis, and have concluded that this name is acceptable. However, if any of the proposed product characteristics as stated in your September 27, 2011, submission are altered, DMEPA rescinds this finding and the name must be resubmitted for review. Additionally, this proprietary name must be re-evaluated 90 days prior to the approval of the application. The conclusions upon re-review are subject to change.

4 REFERENCES

1. ***Micromedex Integrated Index (<http://csi.micromedex.com>)***

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

2. ***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.

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

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products. This database also lists the orphan drugs.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***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.

6. ***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.

7. ***U.S. Patent and Trademark Office (<http://www.uspto.gov>)***

USPTO provides information regarding patent and trademarks.

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

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

9. *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.

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

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

11. *Access Medicine* (www.accessmedicine.com)

Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. *USAN Stems* (<http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml>)

USAN Stems List contains all the recognized USAN stems.

13. *Red Book Pharmacy's Fundamental Reference*

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

14. *Lexi-Comp* (www.lexi.com)

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

15. *Medical Abbreviations Book*

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

16. *CVS/Pharmacy* (www.CVS.com)

This database contains commonly used over the counter products not usually identified in other databases.

17. Walgreens (www.walgreens.com)

This database contains commonly used over the counter products not usually identified in other databases.

18. Rx List (www.rxlist.com)

RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. Dogpile (www.dogpile.com)

Dogpile is a Metasearch engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, 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.). 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.¹

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. 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. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the

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

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 proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, 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. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA 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.² The product characteristics considered for this review appears in Appendix B1 of this review.

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing 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). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

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		
	<i>Potential Causes of Drug Name Similarity</i>	<i>Attributes Examined to Identify Similar Drug Names</i>	<i>Potential Effects</i>
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> 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/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication
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	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA considers the potential for the proposed proprietary 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. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the

safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA searches 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 the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses 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, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Simulation Studies

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.

4. 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.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment 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.³ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, 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 orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product

³ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

characteristics listed in Appendix B1 of this review. 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 Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And Are there any components of the name that may function as a source of error beyond sound/look-alike”

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity or because of some other component of the name. 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, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes 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 not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name 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 the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

- a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP’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 PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. 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)].

- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, 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 but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

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, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, 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, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, 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 approving the error-prone proprietary name. Moreover, even after Sponsors” have changed a product’s proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners” vocabulary, and as a result, 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.

Appendix B: Letters with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Kyprolis	Scripted May Appear as	Spoken May Be Interpreted as
K	R, X	C, Q, Qu, Que, Ques
y	j, u, z, f, p, v, x, z	e, i, u
p	y, ja, jo, g, j, l, q, yn, ys	b, f
r	v, n, s, e, l	-----
o	a, c, e, u	oh
l	e, b, d, t, i, s, A, P	-----
i	c, e, l, r	A, e
s	a, z, x, G, g, n	X, z

Appendix C: Prescription Simulation Samples and Results

Figure 1. Kyprolis Study (Conducted on October 14, 2011)

Handwritten Requisition Medication Order	Verbal Prescription
<p><u>Medication Order:</u></p> <p><i>Kyprolis 40mg IV X1 today</i></p>	<p>“Kyprolis bring 1 vial to clinic”</p>
<p><u>Outpatient Prescription:</u></p> <div style="border: 1px solid black; padding: 5px;"> <p>Patient _____ Date <u>10/13</u></p> <p>Address _____</p> <p>R <i>Kyprolis #1</i></p> <p> <i>bring to clinic</i></p> <p>Refill(s): _____ Dr. <u>OSE</u></p> <p>DEA No. _____ Address _____</p> <p>Telephone _____</p> </div>	

FDA Prescription Simulation Responses

Study Name: Kyprolis

Study Conducted on 10/14/2011 Results As of Date 11/23/2011

85 People Received Study

38 People Responded

Study Name: Kyprolis

INPATIENT	STRENGTH	VOICE	STRENGTH	OUTPATIENT	STRENGTH
KEYPROLIS	40 mg	CHIPROLIS		KYPROLIS	
KYPROLIS	40mg	KIPROLIS		KYPROLIS	
KYPROLIS	40 mg.	KIPROLIS	na	KYPROLIS	
KYPROLIS	40mg	KYPRILIS		KYPROLIS	
KYPROLIS	40mg	KYPROLIS	none	KYPROLIS	
KYPROLIS	40mg	KYPROLIS	one vial	KYPROLIS	
KYPROLIS	40mg	KYPROLIS	1 vial	KYPROLIS	
KYPROLIT	40 mg	KYPROLIS	1 vial	KYPROLIS	
KYPROLIX	40 mg	KYPROLIS		KYPROLIS	
KYPROTES	40mg	KYPROLIS		KYPROLIS	
KYPROTIS	40 mg			KYPROLIS	
KYPROTIS	40 mg			KYPROLIS	
KYPROTIS	40mg				
KYPROTIS	40 mg				
VYPROLIS	40mg				
VYPROLOS	40mg				

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

Proprietary Name	Active Ingredient	Similarity to Kyprolis	Failure preventions
Bystolic	Nebivolol HCl	Look	Lack of convincing orthographic similarity
Hypaque Sodium	Diatrizoate sodium	Look	Lack of convincing orthographic similarity
Hyperal	Intravenous solution of nutrients	Look	Lack of convincing orthographic similarity
HyperHep B	Hepatitis B immune globulin	Look	Lack of convincing orthographic similarity
Hyper-Sal	Sodium chloride	Look	Lack of convincing orthographic similarity
Hypertears	Ocular lubricant	Look	Lack of convincing orthographic similarity
Hypertensa	L-Arginine, L-Glutamine, Histidine (as Histidine HCL), Choline Bitartrate, Dextrose, Cinnamon, Ginkgo Biloba, Grape Seed Extract, Caffeine, Cocoa, Ginseng	Look	Lack of convincing orthographic similarity
Hypertonic Saline	Sodium chloride	Look	Lack of convincing orthographic similarity
Hyphanox	Itraconazole	Look	Lack of convincing orthographic similarity
Kybernin P	Antithrombin III (human)	Look	Lack of convincing orthographic similarity
Kytil	Granisetron HCl	Look	Lack of convincing orthographic similarity This product is not available in the USA. It is only available in Kenya.
Reyataz	Atazanavir	Look	Lack of convincing orthographic similarity
Risperdal	Risperidone	Look	Lack of convincing orthographic similarity
Ryzolt	Tramadol	Look	Lack of convincing orthographic similarity
Victrelis	Boceprevir	Look	Lack of convincing orthographic similarity
Cabergoline	(brand name Dostinex)	Look	Lack of convincing orthographic similarity
Cialis	Tadalafil	Look	Lack of convincing orthographic similarity
Nitrodisc	Nitroglycerin	Look	Lack of convincing orthographic similarity

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

Proprietary Name	Active Ingredient	Similarity to Kyprolis	Failure preventions
Onsolis	Fentanyl	Look	Lack of convincing orthographic similarity
Tacrolimus	(brand name Protopic)	Look	Lack of convincing orthographic similarity
Zyprexa	Olanzapine	Look	Lack of convincing orthographic similarity
Kabolin	(brand name Durabolin)	Look	Lack of convincing orthographic similarity
Kapectolin	Bismuth subsalicylate	Look	Lack of convincing orthographic similarity
Keralac	Urea	Look	Lack of convincing orthographic similarity
Kerlix	Gauze sponge	Look	Lack of convincing orthographic similarity
Kerodex	Non-greasy, water repellent cream	Look	Lack of convincing orthographic similarity
Kerol	Lactic Acid/Salicylic Acid/Urea	Look	Lack of convincing orthographic similarity
Kinerase	Kinetin (moisturizing cream)	Look	Lack of convincing orthographic similarity
Kutrase	Pancrelipase	Look	Lack of convincing orthographic similarity
Key-Plex	Vitamin B ₁ /Vitamin B ₂ /Vitamin B ₃ /Vitamin B ₅ /Vitamin B ₆ /Vitamin B ₁₂ /Vitamin C Injection	Look	This vitamin supplement is not available online or in Redbook and no product characteristics can be found in any of the major drug reference.
Key-Pred	Prednisolone Acetate	Look	This product is not available online or in Redbook and no product characteristics can be found in any of the major drug reference. Preliminary drug usage data confirmed Key-Pred has not been prescribed for the past 5 years.

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

Proprietary Name	Active Ingredient	Similarity to Kyprolis	Failure preventions
K-Y Plus	Nonoxynol-9	Look	This product is a personal lubricant, not a drug product likely to require a prescription.
Kynapid ^{***}	Vernakalant	Look	Kynapid was a proposed name submitted to FDA and approved in 2007. However, the product Vernakalant received an “Approvable” Letter in 2008. The application status at this time is still “Approvable” and the name has not been submitted for any other product.
(b) (4)			
Captopril	(brand name Capoten)	Sound	Lack of convincing phonetic similarity
Ketorolac	(brand name Toradol)	Sound	Lack of convincing phonetic similarity

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

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

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/or use in clinical practice for the reasons described.

<p>Proposed name: Kyprolis (Carfilzomib) Powder for Injection</p>	<p>Strength(s): 60 mg</p>	<p>Usual dose: 20 mg/m² for the first treatment cycle (28 days) and 27 mg/m² for all subsequent cycles intravenously twice weekly</p>
<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p>	<p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p>
<p>Keralyt (Salicylic acid) 6% Gel, Shampoo, Scalp Kit <i>Usual dose:</i> Apply or shampoo as directed by prescriber daily</p>	<p>Orthographic similarity stems from the fact that both names share the same beginning letter (“K”) and the letter “l” in the same position within the name. There is a numerical overlap in strengths (6% and 60 mg).</p>	<p>Keralyt lacks the second downstroke and has an extra upstroke compared to the proposed name, Kyprolis. Therefore, Keralyt looks visually different from Kyprolis when scripted. This overall orthographic difference may help to distinguish this name pair. Both products have different dose and directions for use.</p>
<p>Kyolic (Aged Garlic Extract) 300 mg Capsules 300 mg per ¼ tsp Liquid Extract 1000 mg Caplets <i>Usual dose:</i> Take ¼ or more teaspoonful or one or more capsules or caplets with a meal once to twice daily.</p>	<p>Orthographic similarity stems from the fact that both names share the same beginning letters (“Ky”) and same ending letters of “oli” followed by the letter “s” and “c” that can look similar when scripted. There is a numerical overlap in strengths (60 mg and 600 mg).</p>	<p>Kyolic lacks the second downstroke found in the proposed name, Kyprolis and is shorter in length. Therefore, Kyolic looks visually different from Kyprolis when scripted. This overall orthographic difference may help to distinguish this name pair. Both products have different dose and frequency of administration.</p>

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/or use in clinical practice for the reasons described.

<p>Proposed name: Kyprolis (Carfilzomib) Powder for Injection</p>	<p>Strength(s): 60 mg</p>	<p>Usual dose: 20 mg/m² for the first treatment cycle (28 days) and 27 mg/m² for all subsequent cycles intravenously twice weekly</p>
<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p>	<p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p>
<p>Keppra (Levetiracetam) Tablet, Injection, Concentrate 250 mg, 500 mg, 750 mg, 1000 mg tablets 100 mg/mL oral solution 500 mg/5 mL injection <i>Usual dose:</i> 500 mg, 1000 mg, 2000 mg, and 3000 mg, given as twice daily dosing</p>	<p>Orthographic similarity stems from the fact that both names share the same beginning letter (“K”) and two downstrokes. Both products have same route of administration (intravenously).</p>	<p>Keppra lacks the upstroke found in the proposed name, Kyprolis and is shorter in length. Therefore, Keppra looks visually different from Kyprolis when scripted. This overall orthographic difference may help to distinguish this name pair. Both products have different dose, strength, and frequency of administration.</p>
<p>Caprelsa (Vandetanib) Tablets 100 mg and 300 mg tablets <i>Usual dose:</i> 300 mg orally daily with or without food</p>	<p>Orthographic similarity stems from the fact that both names have the same middle word string “pr” followed by the vowels “o” and “e” that look similar when scripted, and the upstroke letter “l” in the same position. Both products have oncology indications.</p>	<p>Caprelsa lacks the downstroke “y” and has different beginning and ending letters compared to the proposed name, Kyprolis. Therefore, Caprelsa looks visually different from Kyprolis when scripted. This overall orthographic difference may help to distinguish this name pair. Both products have different dose, strength, and directions for use.</p>

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/or use in clinical practice for the reasons described.

<p>Proposed name: Kyprolis (Carfilzomib) Powder for Injection</p>	<p>Strength(s): 60 mg</p>	<p>Usual dose: 20 mg/m² for the first treatment cycle (28 days) and 27 mg/m² for all subsequent cycles intravenously twice weekly</p>
<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p>	<p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p>
<p>Kytril (Granisetron Hydrochloride) Injection Solution, Tablets and Oral Solution</p> <p>0.1 mg/mL, 1 mg/mL, 3 mg/mL single use vials, 4 mg/4 mL multi use vials and</p> <p>1 mg, 2 mg tablets and</p> <p>2 mg/10 mL oral solution</p> <p><u>Usual dose:</u></p> <p>chemo-induced nausea/vomiting: <u>Intravenous dosage:</u> 10 mcg/kg IV within 30 mins before chemotherapy <u>Oral dosage:</u> 1 mg up to 60 mins prior to chemotherapy followed by a second tablet 12 hrs later on the days of chemo or 2 mg as a single dose within 1 hour prior to chemotherapy</p> <p>radiation-induced nausea/vomiting: <u>Oral dosage:</u> 2 mg PO 60 mins prior to radiation.</p> <p>postoperative nausea/vomiting: <u>Intravenous dosage:</u> 1 mg IV push before induction of anesthesia</p>	<p>Orthographic similarity stems from the fact that both names share the same beginning letters (“Ky”).</p> <p>Phonetic similarity stems from the fact that both names share the same beginning syllable from the letter string (“Ky”).</p> <p>Both products can be administered intravenously.</p>	<p>Kytril is shorter in length, lacks the second downstroke “p”, and has an upstroke “t”. Therefore, Kytril looks visually different from Kyprolis when scripted. This overall orthographic difference may help to distinguish this name pair.</p> <p>Kytril has only two syllables compare to Kyprolis with three syllables. Therefore, Kytril sounds different from Kyprolis.</p> <p>Both products have different strength, dose, and frequency of administration.</p>

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/or use in clinical practice for the reasons described.

<p>Proposed name: Kyprolis (Carfilzomib) Powder for Injection</p>	<p>Strength(s): 60 mg</p>	<p>Usual dose: 20 mg/m² for the first treatment cycle (28 days) and 27 mg/m² for all subsequent cycles intravenously twice weekly</p>
<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p>	<p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p>
<p>Kineret (Anakinra) Injection Solution 100 mg/0.67 mL <i>Usual dose:</i> 100 mg/day administered daily by subcutaneous injection</p>	<p>Orthographic similarity stems from the fact that both names share the same beginning letter (“K”) and two upstrokes. Phonetic similarity stems from the fact that both names have three syllables. Both products are injectable products that are administered parenterally.</p>	<p>Kineret lacks the two downstrokes found in Kyprolis and ends with an upstroke “t”. Therefore, Kineret looks visually different from Kyprolis when scripted. This overall orthographic difference may help to distinguish this name pair. Kineret has the letter “n” which lacks phonetic similarity to the letter “p” and lacks the letter “l” found in Kyprolis. Therefore, Kineret sounds different from Kyprolis. Both products have different strength, dose, and frequency of administration.</p>

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/or use in clinical practice for the reasons described.

<p>Proposed name: Kyprolis (Carfilzomib) Powder for Injection</p>	<p>Strength(s): 60 mg</p>	<p>Usual dose: 20 mg/m² for the first treatment cycle (28 days) and 27 mg/m² for all subsequent cycles intravenously twice weekly</p>
<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p>	<p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p>
<p>Kapidex (dexlansoprazole) capsule, delayed release 30 mg, 60 mg capsules <i>Usual dose:</i> 30 mg to 60 mg orally once daily depending on indication</p>	<p>Orthographic similarity stems from the fact that both names share the same beginning letter (“K”), the same letter “p” in the third position, the ensuing letter “r” is similar to letter “i” when scripted, the ensuing letters “ol” is similar to letter “d” when scripted, the ensuing letter “i” is similar to letter “e” when scripted, the ending letter “s” is similar to letter “x” when scripted, and both names share an upstroke letter (“l” vs. “d”) in the same position.</p> <p>Phonetic similarity stems from the fact that both names have three syllables.</p> <p>Both products have overlapping strength and dose.</p>	<p>Kapidex lacks the downstroke from letter “y” found in Kyprolis.</p> <p>Kapidex has a different vowel “a” and ending stress sound from word string “dex”. Therefore, Kapidex sounds different from Kyprolis.</p> <p>Both products have different frequency of administration, directions for use, and storage & handling requirement.</p>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A DE FRONZO
12/08/2011

TODD D BRIDGES
12/08/2011

CAROL A HOLQUIST
12/08/2011