

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-350

PROPRIETARY NAME REVIEW(S)

7/2/09



**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: July 2, 2009

To: Mary Parks , Director
Division of Metabolism and Endocrinology Products

Through: Carol Holquist, R.Ph. Director
Division of Medication Error Prevention and Analysis

From: Melina Griffis, R.Ph., Acting Team Leader
Division of Medication Error Prevention and Analysis

Subject: Proprietary Name Review

Drug Name(s): Onglyza (saxagliptin) Tablets, 5 mg and 

Application Type/Number: NDA 22-350

Applicant/sponsor: Bristol-Myers Squibb

OSE RCM #: 2009-994

1 INTRODUCTION

This review was written in response to notification that the Division of Metabolism and Endocrinology Products is going to take an approval action on this application. The proprietary name Onglyza was last reviewed on February 11, 2009 and found to be acceptable (see OSE review 2008-967).

1.1 PRODUCT DESCRIPTION

Onglyza (Saxagliptin tablets) is a dipeptidyl peptidase 4 (DPP4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The recommended dose of Onglyza is 5 mg once daily with or without food. A single dosage adjustment of 2.5 mg daily is recommended for patients with moderate or severe renal impairment, or end stage renal disease. Onglyza will be available as 2.5 mg and 5 mg oral film-coated tablets. All strengths of Onglyza will be available in bottles of 30 and 90 tablets, and the 5 mg tablets will be available in 500 count bottles and blister packs of 100. Additionally, physicians will be given seven day sample packs of the 5 mg tablets.

2 DISCUSSION

During our final review of the proposed proprietary name, Onglyza, DMEPA identified 13 names not previously reviewed in OSE review 2008-967 (listed in Appendix A). Our FMEA determined that the 13 identified names were unlikely to result in medication errors with Onglyza. Therefore, we have concluded that the proposed proprietary name Onglyza remains acceptable for this product.

3 CONCLUSIONS AND RECOMMENDATIONS

We have completed our review of the proposed proprietary name, Onglyza, and have concluded that it is acceptable. However, if the product approval is delayed beyond 90 day from the date of this memo, the proposed name must be resubmitted for evaluation.

If you have further questions or need clarifications, please contact Mildred Wright, project manager, at 301-796-1027.

Appendix A: Additional names identified and reason to discard

Proprietary Name	Reason to Discard
()	Unapproved orphan designated drug product
()	Unapproved orphan designated drug product
()	Proposed trademarks listed in USPTO but not located in any other drug database
Unga-Eze	Originally identified in Micromedix however, unable to locate in any pharmaceutical database including Micromedix
Angyton	International brand for Amiodarone (marketed in Brazil)
Onyxsan	Withdrawn by Commissioner on 7/24/1970
()	Unapproved drug product as of — no recent activity in DSS
Abilify	Although there is an overlap in dose (5 mg and 10 mg) between Abilify and Onglyza orthographic differences in the names will likely minimize the risk of medication errors. [Abilify contains 3 cross-strokes letters vs 1 for Onglyza. Additionally, Onglyza does not contain any dotted letters and contains one additional downstroke. These names when written are of different shapes.]
Agrylin	Although there is a numerical overlap in dose (5 mg vs 0.5 mg) between Abilify and Agrylin orthographic differences in the names will likely minimize the risk of medication errors. [Abilify contains 3 cross-strokes letters vs 1 for Agrylin. Additionally, Agrylin contains one additional downstroke. These names when written are of different shapes.]
Ony-Clear (1% benzalkonium topical solution)	Different strength availability, dosage form and route of administration

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/s/

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7/2/2009 08:24:25 AM
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 11, 2009

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products

Thru: Kristina Arnwine, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, 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): Onglyza (Saxagliptin) Tablets
2.5 mg and 5 mg

Application Type/Number: NDA # 22-350

Applicant/sponsor: Bristol Myer Squibb

OSE RCM #: 2008-967, 2008-1199

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

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EXECUTIVE SUMMARY

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

In addition, as part of a proprietary name review, the Division of Medication Error Prevention and Analysis reviewed the container labels, carton and insert labeling and noted that improvements could be made to the carton labeling and container label to decrease the potential for selection errors, to minimize confusion with dosing, and to increase readability of information presented on the labeling. DMEPA believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to a request from the Division of Metabolism and Endocrinology Products (DMEP) to evaluate the proposed name, Onglyza, for its potential to contribute to medication errors.

1.2 REGULATORY HISTORY

The IND 63,634 was submitted by Bristol-Myers Squibb on November 8, 2001. The NDA 22-350 for this product was submitted on June 30, 2008. The Division of Medication Error Prevention and Analysis (DMEPA) was consulted on June 11, 2008 to review the proposed proprietary name, Onglyza. Another consult was received from the Division of Metabolism and Endocrine Products on July 23, 2008 to review the label and labeling for Onglyza.

1.3 PRODUCT INFORMATION

Onglyza (Saxagliptin tablets) is a dipeptidyl peptidase 4 (DPP4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The recommended dose of Onglyza is 5 mg once daily with or without food. A single dosage adjustment of 2.5 mg daily is recommended for patients with moderate or severe renal impairment, or end stage renal disease. Onglyza will be available as 2.5 mg and 5 mg oral film-coated tablets. All strengths of Onglyza will be available in bottles of 30 and 90 tablets, and the 5 mg tablets will be available in 500 count bottles and blister packs of 100. Additionally, physicians will be given seven day sample packs of the 5 mg tablets.

2 METHODS AND MATERIALS

This section consists of methods and materials used by medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Label and Labeling Risk Assessment). The primary focus for this assessment is to identify and remedy potential sources of medication error prior to drug approval. 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

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Onglyza, 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 CDER.

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

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure 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.¹ 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. DMEPA 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 Staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

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, the Division of Medication Error Prevention and Analysis 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

2.1.1 Search Criteria

The medication error 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 'O' 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.³⁴

To identify drug names that may look similar to Onglyza, the staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (7 letters), upstrokes (two, capital letter 'O', and 'l'), downstrokes (two, 'g', 'y', possibly three, 'z'), cross-strokes ('z', depending on how scripted), and dotted letters (none). Additionally, several letters in Onglyza may be vulnerable to ambiguity when scripted, including the letter 'O' may appear as 'A'; lower case 'n' appears as a lower case 'v', 'r', or 's'; lower case 'g' may appear as lower case, 'j', 'q' or 'y'; ; lower case 'l' may appear as lower case 't' or 'f'; lower case 'y' may appear as lower case 'j', 'q' or 'g'; lower case 'z' may appear as 'm'; and lower case 'a' appears as lower case 'e', 'o' or 'u'. As such, the staff also considers these alternate appearances when identifying drug names that may look similar to Onglyza.

When searching to identify potential names that may sound similar to Onglyza, the medication error staff search for names with similar number of syllables (three), stresses (ON-gly-za, on-GLY-za or on-gly-ZA), and placement of vowel and consonant sounds. In addition, several letters in Onglyza may be subject to interpretation when spoken, including the letter 'O' may be interpreted as 'A' or 'U'; the letter 'n' may be interpreted as 'm'; the letter 'y' may be interpreted as 'i' or the letter 'z' may be interpreted as 's' or 'c'. The Applicant's intended pronunciation of the proprietary (on-GLY-zah) was also

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

³ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

⁴ Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

taken into consideration, as this was provided by  name review.

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The staff 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, the medication error staff were provided with the following information about the proposed product: the proposed proprietary name (Onglyza), the established name (Saxagliptin), indication (adjunct therapy for type 2 diabetes), strength (2.5 mg, 5 mg), dose (2.5 mg, 5 mg), frequency of administration (once daily), route of administration (oral) and dosage form of the product (film-coated tablet). Appendix A provides a more detailed listing of the product characteristics the medication error staff general takes into consideration.

Lastly, the medication error staff also considers the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Postmarketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the medication error staff 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, Onglyza, was provided to the medication error staff of DMEPA 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 were not identified in the previous reviews that may sound-alike or look-alike to Onglyza 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 medication error staff 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, the medication error staff reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by the Division of Medication Error Prevention and Analysis to gather CDER professional opinions on the safety of the product and the proprietary name, Onglyza. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of the 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

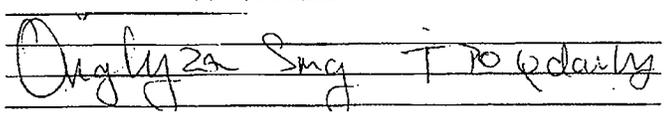
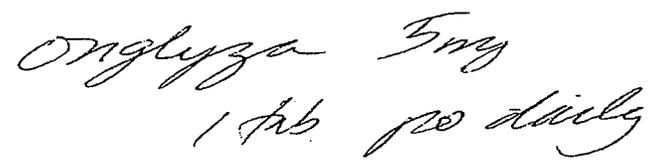
Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 FDA Prescription Analysis Studies

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

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

Figure 1. 0702 Study (conducted on July 11, 2008)

HANDWRITTEN PRESCRIPTION AND MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Inpatient Medication Order:</u></p> 	<p>Onglyza 5 mg One tablet by mouth once daily</p>
<p><u>Outpatient Medication Order:</u></p> 	

2.1.3 External Proprietary Name Risk Assessments

For this product, the Applicant submitted two name validation studies to evaluate the proposed proprietary name Onglyza. One study was conducted by (

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and one study was conducted by _____

The Division of Medication Error Prevention and Analysis conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessments. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in the Division's medication error staff's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the Safety Evaluator has determined the overall risk assessment of the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Sponsor. The Safety Evaluator then determines whether the Division's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, DMEPA provides a detailed explanation of these differences.

2.1.4 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode 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.⁵ 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 than 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 Onglyza convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer

⁵ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

indicates a failure mode and represents a potential for Onglyza 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 provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

The Division of Medication Error Prevention and Analysis 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. The Division of Medication Error Prevention and Analysis 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 and another drug product.

In the event that the Division of Medication Error Prevention and Analysis objects to the use of the proposed proprietary name, based upon the potential for confusion with another

proposed (but not yet approved) proprietary name, the Division will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use the name, while the Division will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then the Division of Medication Error Prevention and Analysis will not object to the use of the proprietary name. If any of these conditions are met, then the Division will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Sponsor; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the IOM, WHO, JCAHO, and ISMP, 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, the Division of Medication Error Prevention and Analysis 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 Sponsor, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Sponsor's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, the Division of Medication Error Prevention and Analysis 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 the Division of Medication Error Prevention and Analysis 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. The Division of Medication Error Prevention and Analysis is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for the Division of Medication Error Prevention and Analysis 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 the Division of Medication Error Prevention and Analysis may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, 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 errors⁶ 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 June 30, 2008 the Applicant submitted the following labels for our review:

- Container Labels: (Appendix J)
- Blister Label: (Appendix K)
- Carton Labeling: (Appendix L)
- Package Insert Labeling (no image)

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

For this review, the medication error staff identified 16 names as having some similarity to the name Onglyza. The names Enjuvia, (C,) Ansolysen, Onglipa, Fuglyza, Angeliq, Proglycem, Angiovist, (Anglo, (and () were thought to look like Onglyza. Longlyza and Yonglida were thought to sound like Onglyza. The two remaining names, Onglinex and Onglyza were thought to look and sound like Onglyza.

A search of the United States Adopted Name stem list on September 15, 2008 identified no USAN stem names within the proposed name, Onglyza.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by DMEPA (see section 3.1.1. above), but did not identify any additional names with similarity to Onglyza.

⁶ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

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 FDA Prescription Analysis Studies

A total of 33 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. About 85% of the participants (n=28) interpreted the name correctly as "Onglyza," with correct interpretation occurring more frequently in the written studies. The majority of misinterpretations occurred in the phonetic prescription study, and misinterpreted the 'O' as a 'U' and the 'y' as an 'i'. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 External Proprietary Name Risk Assessments

The Applicant provided two proposed name validation studies conducted by ()
() respectively, to assess the proposed proprietary name, Onglyza. Neither () identified any names that would result in confusion with the proposed proprietary name, Onglyza.

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3.1.5 Safety Evaluator Risk Assessment

Independent searches by the primary safety evaluator resulted in one additional name, Aryplase, which was thought to look similar to Onglyza and represent a potential source of drug name confusion. As such, a total of 17 names were analyzed to determine if the drug names were reviewed for look alike and sound alike similarity and if the drug name confusion would likely result in a medication error.

All of the identified names were thought to have some orthographic and/or phonetic similarity to Onglyza, and thus were determined to present some risk of confusion. Failure Mode and Effects analysis (FMEA) was then applied to determine if the proposed name, Onglyza, could potentially be confused with any of the 17 names and lead to medication error.

This analysis determined that the name similarity between Onglyza and the identified names was unlikely to result in medication errors for all 17 product names for the reasons listed in Appendix C through Appendix J.

3.2 LABEL AND LABELING RISK ASSESSMENT

Upon review of the container labels, carton and insert labeling DMEPA identified several areas of vulnerability that could lead to medication errors.

3.2.1 Container Label

The font size in addition to the background and foreground colors chosen decrease the readability of the established name on the 2.5 mg strength container label.

3.2.2 Sample Blister Folder Label

There is a graphic presented in the proposed proprietary name on the sample blister folder.

The statement “each tablet contains 5 mg” is located on the back of the sample, rather than next to the blisters containing the tablets.

The 5 mg strength is not prominently placed on the physician blister folder.

The dosage form, tablet, should follow the established name.

The dosage form and strength act as intervening matter due to its placement after the proposed proprietary name and before the established name on the sample blister folder.

The pills in the physician sample blister folder are placed in a vertical manner, rather than a horizontal manner.

3.2.3 Sample Tray

There is a graphic display on the proposed proprietary name on the physician sample tray labeling

The 5 mg strength is not prominently placed on the physician sample tray labeling.

The dosage form and strength is placed in between the proposed proprietary name and the established name on the physician sample tray labeling.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

We evaluated a total of 18 names for their potential confusion with Onglyza. Our FMEA determined that the proposed name is not vulnerable to name confusion that could lead to medication errors. This finding was consistent with and supported by the two independent risk assessments of the proprietary name submitted by the Sponsor.

4.2 LABEL AND LABELING REVIEW

Our analysis identified several areas of needed improvement that could lead to medication errors.

4.2.1 2.5 mg, 30 and 90 count Container Label

The established name, Saxagliptin, is presented in a white, fine font which makes it difficult to read. Although the established name is ½ the size of the proprietary name, the established name does not have a prominence commensurate with the proprietary name. Revising the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10 (g)(2) will improve the prominence of the established name.

4.2.2 Sample Blister Folder Tray Labeling and Sample Blister Labeling

4.2.2.1 Presentation of the Proprietary Name, Dosage Form and Strength

The dosage form and strength lack prominence because they are positioned between the proposed proprietary name and the established name (on the tray label and physician sample label) and are presented in a small font. A more prominently displayed strength, in the format of ‘5 mg per tablet’ will adequately communicate to the patient that each tablet

contains 5 mg and avoid any confusion regarding strength per tablet vs. total mg per package. Additionally, the established name should be followed by the dosage form and be presented on the label as Saxagliptin Tablets.

The dosage form and strength act as intervening matter between the proprietary name and the established name. The proposed presentation is not in accordance with labeling regulations. The presentation on the folder tray labeling and the sample blister labeling should be revised to be in accordance with 21 CFR 201.57(a)(2) which states the presentation on the label should consist of the proprietary name immediately followed by the established name followed by the drug's dosage form.

Additionally, the middle letters (gly) of the proprietary name are presented in a lighter font that make the proprietary name look like three separate entities (i.e., **onglyza**). As noted above presenting the name in the same manner on the sample blister label and carton as it is on the trade container label will improve readability.

4.2.3 Sample Blister Folder Label - Days of the Week Presentation

The pills in the sample blister label are labeled with days 1 through 7. However they are numbered in a vertical manner which may be confusing to patients as patients intuitively read from left to right. The relevance of numbering is lessened as it does not matter how patients remove this drug from the sample blister as no titration is necessary and the dose remains consistent each day. Thus, deleting days 1 through 7 from the blister would be less confusing and result in less clutter on the blister label.

5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Onglyza, is not vulnerable to name confusion that could lead to medication errors. This finding was consistent with and supported by two independent risk assessments of the proprietary name submitted by the Sponsor. As such, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Onglyza, for this product.

If **any** of the proposed product characteristics as stated in this review are altered prior to approval of the product, the Division of Medication Error Prevention Analysis rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the blister pack and tray labeling introduces vulnerability to confusion that could lead to medication errors. We believe the risks identified can be addressed and mitigated prior to drug approval, and provide recommendations in Section 6.B.

5.1 COMMENTS TO THE DIVISION

We would appreciate feedback on the final outcome of this review. Please copy us on any communication to the Applicant with regard to this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Cheryl Campbell, Project Manager, at 301-796-0732.

5.2 COMMENTS TO THE APPLICANT

A. Proposed Proprietary Name Review

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

The proposed proprietary name, Onglyza, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics area altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

B. Label and Labeling Risk Assessment

1. 2.5 mg; 30 and 90 Count Container Label

Revise the prominence of the established name to ensure that it is ½ the size of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10 (g)(2) which will improve the prominence of the established name.

2. Sample Blister Folder Label and Sample Tray

- a. Relocate the dosage form and strength to be in accordance with CFR 21 CFR 201.57(a)(2) so that it is not located between the proposed proprietary name and the established name. We also recommend increasing the prominence of the 5 mg per tablet statement by increasing the size and font on the primary display panel. This will increase the visibility of the strength and dosage form and make this pertinent information more readily accessible to practitioners.
- b. The dosage form should directly follow the established name, i.e. Saxagliptin Tablets.
- c. Improve the readability of the proprietary name, Onglyza, by removing the lighter font on the middle letters, **gly**. We recommend replicating the presentation of the name on the trade container label.
- d. Delete the numbered days on the blister folder as they are presented in a non-intuitive manner (i.e., vertical rather than horizontal). The tablets in this packaging configuration do not have to be taken in a specific order and thus do not require the numbered days of the week which may be confusing to the patients.

6 REFERENCES

1. ***Micromedex Integrated Index*** (<http://weblern/>)

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

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

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

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

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

4. ***AMF Decision Support System [DSS]***

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

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

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

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 and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, discontinued drugs and “Chemical Type 6” approvals.

7. ***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.

8. ***WWW location*** <http://www.uspto.gov>.

Provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (<http://weblern/>)

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

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

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

11. Natural Medicines Comprehensive Databases (<http://weblern/>)

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

12. Stat!Ref (<http://weblern/>)

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

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

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

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

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions

APPENDICES

Appendix A:

The medication error staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. The Division of Medication Error Prevention 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 examines 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 applies 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 compares 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 Sponsor’s intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, the Division of Medication Error Prevention 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	<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	<p>Similar spelling</p> <p>Length of the name</p> <p>Upstrokes</p> <p>Downstrokes</p> <p>Cross-strokes</p> <p>Dotted letters</p> <p>Ambiguity introduced by scripting letters</p> <p>Overlapping product characteristics</p>	<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	<p>Identical prefix</p> <p>Identical infix</p> <p>Identical suffix</p> <p>Number of syllables</p> <p>Stresses</p> <p>Placement of vowel sounds</p> <p>Placement of consonant sounds</p> <p>Overlapping product characteristics</p>	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: CDER Prescription Study Responses- Study

Inpatient Medication Order	Voice Prescription	Outpatient Medication Order
Onglyza	Ongliza	Onglyza
Onglyza	Onglyza	Onglyza
Onglyza	Ongliza	Onglyza
Onglyza	Onglyza	Onglyza
Onglyza	Unglyza	Onglyza
Onglyza	Ongliza	Onglyza
Onglyza	Unglyza	Onglyza
Onglyza		Onglyza
Onglyza		Onglyza
		Onglyza

Appendix C: Name registered internationally

Proprietary Name	Similarity to Onglyza	Source	Country
Onglinex	Look and Sound	Saegis	Portugal

Appendix D: Unable to find name on any internet or commonly used reference source

Proprietary Name	Similarity to Onglyza	Source
Fuglyza	Look	USPTO

Appendix E: Name Safety Evaluator unable to identify as a drug

Name Reported in EPD	Correct Spelling	Source Where Name Found
Anglo	Anglo-Scandinavian Study	Stat!Ref

Appendix F: Proprietary name registered with USPTO, however no drug or product is associated with name, or registered name is Onglyza

Proprietary Name	Similarity to Onglyza	Company	Source
Onglipa	Look	Bristol-Myers Squibb	USPTO
Longlyza	Look	Bristol-Myers Squibb	USPTO
Yonglida	Look	Changshu Yudong Chemical Factory	USPTO
Onglyza	Look and Sound	Bristol-Myer's Squibb	USPTO

Appendix G: Product withdrawn from market with no generic equivalent products available

Proprietary Name	Similarity to Onglyza	Status/Date
Ansolsen (Pentolinium tartrate)	Look	Withdrawn by Commissioner November 5, 1992

Appendix H: Drug name denied approval by DDMAC, Division concurred with DDMAC and new name proposed

Name/Application #	Similarity to Onglyza	Source Where Name Found
	Look	AIMS proposed names ()

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Appendix I: Product Characteristics of names with no numerical overlap in dose or strength

Product name with potential for confusion	Similarity to Onglyza	Strength	Usual Dose (if applicable)
Onglyza (Saxagliptin)		2.5 mg, 5 mg oral film-coated tablets	Usual dose: 5 mg orally once daily
Angiovist 282 (Diatrizoate meglumine)	Look	60 %	Angiovist has been discontinued and is now marketed under various names; Cardiografin, Cystografin, Gastrografen, Gatrovist, Hypaque, MD-50, MD-60, MD-76, MD-76R, MD-
Angiovist 292 (Diatrizoate		52 %; 8 %	

Product name with potential for confusion	Similarity to Onglyza	Strength	Usual Dose (if applicable)
Onglyza (Saxagliptin)		25 mg, 5 mg oral film-coated tablets	Usual dose: 5 mg orally once daily
meglumine; Diatrizoate sodium) Angiovist 370 (Diatrizoate meglumine; Diatrizoate sodium) Status: Angiovist is discontinued		66 %; 10%	Gastroview, Reno-30, Reno-60, Renografin-60, etc Diatrizoate meglumine; Fill bladder to capacity with 25 mL to 300 mL prior to procedure Diatrizoate sodium; 30 mL intravenously, may be repeated in 15 to 30 minutes if satisfactory visualization has not been achieved
	Look		
	Look		
Angeliq (Drospirenone/Estradiol)	Look	0.5 mg/1 mg oral tablet	One tablet orally once daily for menopausal symptoms

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Appendix J: Names of products with overlap in dose or strength but differentiating frequency of administration or length of therapy

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Other differentiating product characteristics
Dingyza (Saxagliptin)		25 mg, 50 mg oral film-coated tablets	Usual dose: 5 mg orally once daily	
Proglycem (Diazoxide)	Look	50 mg, 100 mg oral capsule 50 mg/mL oral suspension	Adults and Children: 3 mg/kg to 8 mg/kg divided into two or three equal doses Infants and Newborns: 8 mg/kg to 15 mg/kg divided into two or three equal doses	Frequency (once daily vs. two to three times daily) Dose (2.5 mg or 5 mg vs. weight based)
S S	Look	S		S

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Appendix K: Potential for name confusion with overlap in dose or strength and frequency but with phonetic/orthographic and product characteristic differences

<p>Onglyza (Saxagliptin)</p>	<p>2.5 mg, 5 mg oral film-coated tablets</p>	<p>Usual dose: 5 mg orally once daily</p>
<p>Failure Mode: (Name confusion)</p>	<p>Causes (could be multiple)</p>	<p>Effects</p>
<p>Enjuvia (Conjugated Estrogen) 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg oral tablets Dose : 0.3 mg to 1.25 mg orally once daily</p>	<p>Numerical overlap in achievable dose (2.5 mg and 5 mg tablets vs. 1.25 mg tablets) Frequency (once daily) Route of administration (oral) Orthographic similarities (both contain seven letters, both have a down stroke as third letter and both end in 'a')</p>	<p>Medication errors are unlikely due to the orthographic differences as well as differentiating product characteristics. Orthographically Onglyza contains two downstrokes with one upstroke in between the downstrokes 'gly' vs. one down stroke in Enjuvia and no upstrokes. Enjuvia also contains one dotted letter (possibly two, depending on scripting of 'j'). The initial letter of Onglyza 'O' does not resemble the initial letter of 'E' in Enjuvia. The patient population for Enjuvia will be exclusively female which would indicate an error if a man were to be prescribed Enjuvia. The maximum dose recommended for Enjuvia is 1.25 mg once daily, the lowest dose available for Onglyza is 2.5 mg and the tablet is film coated which discourages tablet splitting or makes tablet splitting difficult. This would prompt the physician, pharmacist or patient to verify the medication and dose as it is very difficult to obtain a consistent dose from splitting an un-scored tablet thereby preventing a medication error.</p>

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