

2.1.1 Search Criteria

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

For this review, particular consideration was given to drug names beginning with the letter '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.⁴⁵

To identify drug names that may look similar to Onsolis, the Staff also consider the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (7 letters), upstrokes (1, capital letter 'O'), downstrokes (none), cross-strokes (none), and dotted letters ('i'). Additionally, several letters in Onsolis may be vulnerable to ambiguity when scripted, including the letter 'O' may appear as 'A', 'C', 'D', or 'U'; lower case 'n' appear as a lower case 'r' or lower case 's'; lower case 's' appear as a lower case 'r' or 'n'; lower case 'o' appear as lower case 'a' or lower case 'u'; and '-lis' may appear as '-les'. As such, the Staff also consider these alternate appearances when identifying drug names that may look similar to Onsolis.

When searching to identify potential names that may look or sound similar to Onsolis, the Medication Error Staff search for names with similar number of syllables (three), stresses (on-SO-lis or ON-so-lis), and placement of vowel and consonant sounds. The Sponsor's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also 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 (Onsolis), the established name ' _____ ', proposed indication (breakthrough cancer pain), strength (200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg), dose (varies dependent of dose efficacy and tolerance), frequency of administration (as needed up to four times daily), route (buccal) and dosage form of the product (bioerodible mucoadhesive system). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff general take into consideration.

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

2.1.1.1 Databases and information sources

The proposed proprietary name, Onsolis, was provided to the medication error staff of DMETS to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Onsolis using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is

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

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

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

2.1.1.2 CDER Expert Panel Discussion

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

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

2.1.2 CDER Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Onsolis 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 Onsolis 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. Onsolis Study (conducted on September 25, 2007)

HANDWRITTEN PRESCRIPTION AND MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Outpatient Prescription:</u></p> <p>Onsolis 400mg #120 1 tab po QID</p>	<p>Onsolis 400 mg Dispense # 120 1 tablet by mouth four times daily</p>
<p><u>Inpatient Medication Order:</u></p> <p>Onsolis 400mg 1 po qid</p>	

2.1.3 External Proprietary Name Risk Assessment

For this product, the Sponsor submitted an independent risk assessment of the proposed proprietary name conducted by a consulting firm. DMETS conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in the DMETS 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 DMETS's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, DMETS 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 applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁶ When applying FMEA to assess the risk of a proposed proprietary name, DMETS seeks to evaluate the potential for a

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

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 Onsolis convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Onsolis 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.

DMETS will object to the use of proposed proprietary name when 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. DMETS 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. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug another drug product.

In the event that DMETS objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMETS 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 DMETS will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then DMETS will not object to the use of the proprietary name. If any of these conditions are met, then DMETS 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/Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the 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, DMETS 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, DMETS 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 (e.g. new form introduced like Lamisil) (see limitations of the process).

If DMETS 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. DMETS is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for DMETS 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 DMETS may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Data base and information sources

DMETS conducted a search of the internet, several standard published databases and information sources (see Section 7 References) for existing drug names which sound-alike or look-alike to Onsolis to a degree where potential confusion between drug names could occur and result in medication errors in the usual

clinical practice settings. In total, nine names were identified as having some similarity to the name Onsolis.

Seven of the nine names were thought to look like Onsolis, which include: Anusol HC, Onxol, Cialis, _____ Oncovin, Orudis, and Ionsys. One name, Mycelelex, was thought to sound like Onsolis. One additional name, Insulin, was thought to look and sound similar to Onsolis.

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3.1.2 Expert panel discussion

The Expert Panel reviewed the pool of names identified by DMETS staff (see section 3.1.1. above), and did not note any additional names thought to have orthographic or phonetic similarity to Onsolis and have the potential for confusion.

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

3.1.3 CDER Prescription analysis studies

A total of 28 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. About 30% of the participants (n=8) interpreted the name correctly as "Onsolis," with correct interpretation occurring more frequently in the inpatient written study. The remainder of the responses (n=20) misinterpreted the drug name. The majority of misinterpretations occurred in the outpatient written study, with the first letter 'O' reported as a 'G', the second letter 'o' in Onsolis reported as 'a' and/or the letter 'n' reported as 'r'. In the verbal prescription studies, the proposed name was misinterpreted as "Omsolace", "Onsolun", and "Opsolin". See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 External Name studies

In the proposed name risk assessment submitted by the Sponsor _____, identified and evaluated a total of nine drug names thought to have some potential for confusion with the name Onsolis.

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Five of the nine names were not previously identified in DMETS Staff searches, the Expert Panel Discussion, or FDA prescription studies. Three names (Solia, Atacand, Oxycontin) were thought by practitioners to sound similar to Onsolis. Two names (Ambien, Orasone) were thought by practitioners to look similar to Onsolis.

3.1.5 Safety Evaluator Risk Assessment of Proposed Proprietary Name

Independent searches by the primary Safety Evaluator did not identify any additional names thought to look similar to Onsolis and represent a potential source of drug name confusion. As such, a total of 14 names were analyzed to determine if the drug names could be confused with Onsolis, and if the drug name confusion would likely result in a medication error.

All of the identified names were determined to have some orthographic and/or phonetic similarity to Onsolis, and thus determined to present some risk for confusion. Failure modes and effects analysis was then applied to determine if the proposed name, Onsolis, could potentially be confused with any of the 14 names and lead to medication error.

This analysis determined that the name similarity between Onsolis and the identified names was unlikely to result in medication errors for all 14 products. One proprietary name _____ could not be found in commonly used drug references such as Clinical Pharmacology Online, Facts & Comparisons, Micromedex, STATRef, the Orange Book, or the Red Book and thus determined by FMEA to pose minimal risk for error in the usual practice setting.

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For seven of the names identified (Anusol HC, Oncovin, Orudis, Mycelelex, Ambien, Solia, Atacand), FMEA determined that medication errors were unlikely because the products do not overlap in strength or dosage with Onsolis and have minimal orthographic and/or visual similarity to Onsolis (Appendix D). Onsolis is proposed to be marketed in five strengths (200 mcg, 400 mcg, 600 mcg, 800 mcg, and 1200 mcg); the strength or dosage of the product most likely will be included in written and verbal prescriptions under typical conditions of practice which we determined will help to differentiate the products.

Six names (Onxol, Cialis, Ionsys, Insulin, Orasone, Oxycontin) had some numerical overlap with Onsolis in either dosage or strength, but analysis of the failure mode did not determine the effect of this similarity to result in medication errors in the usual practice setting (see Appendix E).

4 DISCUSSION

The results of the Proprietary Name Risk Assessment found that the proposed name, Onsolis, has some similarity to other proprietary and established drug names, but the findings of the FMEA indicate that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Sponsor.

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

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics, future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit our findings. To help counterbalance this impact, DMETS recommends that the proprietary name be re-submitted for review if approval of the product is delayed beyond 90 days.

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

5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Onsolis, does not appear to be vulnerable to name confusion that could lead to medication errors. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Sponsor. As such, DMETS does not object to the use of the proprietary name, Onsolis, for this product. Additionally, DDMAC does not object to the proposed name, Onsolis from a promotional perspective.