

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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22-332

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**

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To: Norman Stockbridge, M.D.
Director, Division of Cardiovascular and Renal Products

Through: 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 Review

Drug Name: Adcirca (Tadalafil) Tablets, 20 mg

Application Type/Number: IND 71,871 · NDA 22-332

Applicant: Eli Lilly

OSE RCM #: 2008-139

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

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EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Adcirca, is not vulnerable to name confusion that could lead to medication errors. Thus, we have no objections to the use of the proprietary name, Adcirca, for this product.

As part of a proprietary name review, the Division of Medication Error Prevention and Analysis reviewed the container label and insert labeling and noted that improvements could be made to the container label to decrease the potential for selection errors, to minimize confusion with dosing, and to increase readability of information presented on the labeling. The risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5 that aim at reducing the risk of medication errors

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Cardiovascular and Renal Products to evaluate the proposed proprietary name for its potential to contribute to medication errors. The proprietary name, Adcirca, is evaluated to determine if the name could be potentially confused with other proprietary or established drug names. Additionally, labels were submitted for risk assessment and overall evaluation of product information and clarity. The sponsor submitted an independent analysis of the name conducted by _____

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1.2 REGULATORY HISTORY

The sponsor submitted the name Adcirca for review on January 10, 2008. Adcirca contains the same active ingredient as Cialis (tadalafil), and thus would be considered a dual proprietary name. Cialis was approved on November 21, 2003.

The Applicant proposes to market Tadalafil tablets with a new indication of use, pulmonary arterial hypertension, under the proprietary name Adcirca. The Applicant currently markets Tadalafil tablets under the proprietary name Cialis, which has been marketed since its approval on November 23, 2003, for use in patients with erectile dysfunction (NDA 21-368).

1.3 PRODUCT INFORMATION

Adcirca is being developed for the treatment of pulmonary arterial hypertension (PAH). The usual dose is 40 mg once daily. No titration is required; however doses should be decreased to 20 mg once daily for mild to moderate renal and hepatic impairment. The product will be available as an oral tablet in the dosage strength of 20 mg and available in a bottle of 60 tablets.

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

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by DMEPA staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling and/or package risk assessment (see 2.2 Container Label, Carton and Insert 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, Adcirca, and the proprietary and established names of drug products existing in the marketplace and those pending BLA, IND, NDA, and ANDA products currently under review by the CDER.

DMEPA searches 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 a CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.2). We also conduct internal CDER prescription analysis studies (see 2.1.3), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.3).

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 2.1.6). This assessment also had to take into consideration the implications of introducing a dual trade name to the market which involves assessing scenarios which may present the prescribing of both drugs at the same time and the adverse events which may ensue. 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. We define a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.² We use the clinical expertise of our DMEPA 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.

² National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

As such, DMEPA considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed name may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication 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.

Because drug name confusion can occur at any point in the medication use process, we consider the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.³

2.1.1 Search Criteria

DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'A' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.^{4,5}

To identify drug names that may look similar to Adcirca, DMEPA also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), upstrokes (two, 'A' and 'd'), capital letter (one, 'A'), downstrokes (none), cross-strokes (one, 'A'), and dotted letters (one, 'i').

Additionally, several letters in Adcirca may be vulnerable to ambiguity when scripted, including the letter 'A' which may appear similar to 'O' or 'I' and to lower case pairs 'ce', 'cl', 'ci'; the letter 'd' may appear as 'cl'; lower case 'c' may appear as a lower case 'a' or 'r'; lower case 'ci' may appear as a lower case 'a' or 'u'; lower case 'r' may appear as a lower case 'n', 'v', 'u', or 's'; lower case 'a' may appear as a lower case 'u', 'c', 'ci' and 'ce'. As such, DMEPA also considers these alternate appearances when identifying drug names that may look similar to Adcirca.

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

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

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

When searching to identify potential names that may sound similar Adcirca, DMEPA searches for names with similar number of syllables (three), stresses (AD-cir-ca, ad-CIR-ca, or ad-cir-CA), and placement of vowel and consonant sounds. In addition, several letters in Adcirca may be subject to interpretation when spoken, including the letter 'c' may be interpreted as 's', 'z' or 'k', and the letters 'ci' may be interpreted as 'su', 'se', or 'si'. As such, DMEPA also considers these alternate pronunciations when identifying drug names that may sound similar to Adcirca. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

DMEPA also considers the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the DMEPA staff were provided with the following information about the proposed product: the proposed proprietary name (Adcirca), the established name (tadalafil), proposed indication (pulmonary arterial hypertension), strength (20 mg), dose (40 mg), frequency of administration (once daily), route of administration (oral) and dosage form of the product (tablets). Appendix A provides a more detailed listing of the product characteristics that the medication error staff typically take into consideration.

2.1.2 Database and Information Sources

The proposed proprietary name, Adcirca, was provided to 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 may sound-alike or look-alike to Adcirca using the criteria outlined in 2.1. A standard description of the databases used in the searches is provided in Appendix A. 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, DMEPA 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.

2.1.3 CDER Expert Panel Discussion

An Expert Panel Discussion is held to gather CDER professional opinions on the safety of the product and the proprietary name, Adcirca. 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).

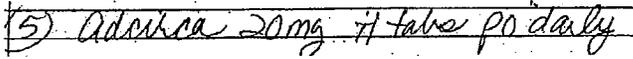
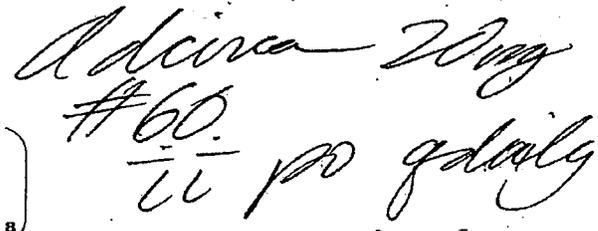
The pooled results of the DMEPA staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general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

2.1.4 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 Adcirca 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 Adcirca in handwriting and verbal communication of the name, inpatient medication orders 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 DMEPA staff.

Figure 1. Adcirca Study 0227 (conducted on February 26, 2008)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Inpatient Written Prescription:</u></p> 	<p>Adcirca, 20 mg, #60. Take 2 tablets by mouth daily.</p>
<p><u>Outpatient Written Prescription:</u></p> 	

2.1.5 External Proprietary Name Risk Assessment

For this product, the Applicant submitted an independent risk assessment of the proposed proprietary name Adcirca. 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 assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in the DMEPA 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 Applicant. The Safety Evaluator then determines whether our risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, we provide a detailed explanation of these differences.

2.1.6 Adverse Event Reporting System (AERS) Selection of Cases

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

The FDA Adverse Event Reporting System (AERS) was searched on July 3, 2008 and May 13, 2009 to assess errors associated with Revatio and Viagra and how they could relate to Adcirca and Cialis due to product similarities between Adcirca and Revatio (i.e. both products are a dual proprietary name for which the original products, Cialis and Viagra, are indicated for erectile dysfunction, and the subsequent names are for pulmonary arterial hypertension). The AERS search conducted on July 3, 2008 used the MedDRA Higher Level Terms (HLT) “Maladministration”, “Medication Errors NEC”, “Medication Errors Due to Accidental Exposures”, “Medication Monitoring Errors”, and the Preferred Terms (PT) “Overdose”, “Accidental Overdose”, “Multiple Drug Overdose”, “Multiple Drug Overdose Accidental”, and verbatim substance names “Reva%” and tradename “Revatio” were used as search criteria. The AERS search conducted on May 13, 2009 utilized the tradename “Revatio” and a broader search of the reports which did not limit adverse events with terms. The narratives from these cases were scanned for adverse events that may have resulted from therapy with any nitro containing molecules.

The cases were manually reviewed to determine if a medication error occurred. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors

2.1.7 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 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.⁶

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

When applying FMEA to assess the risk of a proposed proprietary name, the DMEPA staff 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 Adcirca 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 Adcirca 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 the following questions:

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

“Is it less confusing to market this product under the same name or two different names?”

The answers to these questions are 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.

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

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

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

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Sponsor, and at the expense of the public welfare, not to mention the Agency's credibility as the authority

responsible for the approving the error-prone proprietary name. Moreover, even after Sponsor's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, we believe that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

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

2.2 LABEL AND LABELING RISK ASSESSMENT

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

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

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

For this product the Applicant submitted on September 11, 2008 the following labels and labeling for the DMEPA staff review (see Appendix I)

- Container label: 20 mg
- Package Insert (no image)

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

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

For this review, DMEPA identified 19 names as having some similarity to the name Adcirca. The names Aducil, Advair, Adoxa, Codeine, Arcoxia, Alinia, Aldara, Circanol, Arnica, Cialis, Ciclopirox, Cidex and Ceclor were thought to look like Adcirca. The names Adacel and Akurza were thought to sound similar like Adcirca and the names Concerta, Advicor, Dynacirc and Adcirqa were thought to look and sound like Adcirca.

A search of the United States Adopted Name (USAN) stem list on May 14, 2009 identified no USAN stem names within the proposed name, Adcirca.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the DMEPA staff (see section 3.1 above), and noted no additional names.

The Safety Evaluator was told of the dual proprietary name with Revatio and Viagra and referred to those reviews for insight into the dual proprietary name issue. The Expert Panel recommended that an AERS search be conducted to evaluate medication errors associated with Revatio and Viagra to see if they are applicable to Adcirca and Cialis.

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, and none of the responses overlapped with any existing or proposed drug names. Eighty-eight percent of the participants (n=29) interpreted the name correctly as "Adcirca," with correct interpretation occurring more frequently in the written outpatient studies. The remainder of the responses misinterpreted the drug name.

The majority of misinterpretations occurred in the voice study, with the first letter 'c' being misinterpreted as 's', the letter 'i' being misinterpreted as the letter 'e', and the second letter 'c' being misinterpreted as the letter 'k' for a total of 3 respondents. The other misinterpretations occurred in the outpatient requisition order where the second letter 'c' was omitted from the name. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 External Proprietary Name Risk Assessment

In the submission the applicant provided a proposed name validation study conducted by _____ in the proposed name risk assessment submitted by the applicant, the _____ Inc. identified two names that look or sound similar to the proposed proprietary name, Adcirca. The following two names were identified by _____; Advicor and Advair. These two names were also identified by our DMEPA staff searches. _____ did not address the dual trade name issues in their review.

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3.1.5 Adverse Event Reporting System (AERS)

The FDA Adverse Event Reporting System (AERS) search conducted on July 3, 2008 yielded four cases involving adverse events and medication errors associated with the use of Revatio. However, none of the four cases involved medication errors between Revatio and Viagra. Two cases involved adverse events associated with Revatio. The remaining two cases involved name confusion between Revatio and Revia and thus, are not pertinent to this review.

The broader AERS search conducted on May 13, 2009 yielded 287 cases. Out of the 287 cases, only 10 cases had 'nitr' in the narrative and only one case involved a scenario where the patient was administered Nitroprusside while on Revatio therapy. This occurred in a hospital setting and no adverse event was reported as a result of this medication error.

3.1.6 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Neither DDMAC nor the Division of Cardiovascular and Renal Products had concerns with the proposed proprietary name, Adcirca.

Independent searches by the primary Safety Evaluator identified three additional names thought to look similar to and represent a potential source of drug name confusion to Adcirca (Climara, Aclaro, and Alora). As such, a total of twenty-two names were identified by DMEPA and ~~_____~~

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Eight of the twenty-two names were determined to lack orthographic and/or phonetic similarity, therefore were not analyzed further.

Failure modes and effects analysis (FMEA) was then applied to determine if the proposed name, Adcirca, could potentially be confused with any of the remaining 14 names and lead to medication error. FMEA determined that the name similarity between Adcirca and the identified names was unlikely to result in medication errors for all 14 products. See Appendices D through G for our evaluation of the 14 products identified.

Additionally, we evaluated failures that might occur if the product was marketed under two different proprietary names. Giving consideration to the product differences in dosing regimens, product strengths and total daily dose, as part of the FMEA, this analysis determined that having this product marketed as both a single name or dual names provided opportunity for failures that could lead to confusion in the usual practice place. However, this analysis determined the presence of two names offered an additional failure mode not seen with the single name. This failure mode could result in the concomitant administration of Tadalafil (see section 4.1 for full discussion).

3.2 LABEL AND LABELING RISK ASSESSMENT

There is no dosage form after the established name.

We note there is no statement that alerts providers and patients that Adcirca contains the 'same active ingredient as Cialis'.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

This evaluation not only considered the potential for Adcirca to be confused with currently marketed products or products in the pipeline, but also potential risk with the use of a dual name for Tadalafil.

Our evaluation identified 22 names as having potential similarity to the proposed name Adcirca. The FMEA analysis of the 22 names determined low vulnerability to confusion. The FMEA of the use of two different proprietary names indicated that there is a potential for concomitant administration of Cialis and Adcirca. This type of error may be undetectable because patients and practitioners may not realize that the products contain the same active ingredients.

Since Revatio and Viagra are currently dual proprietary names for sildenafil and the approved indications of Revatio and Viagra are similar to those for Cialis and Adcirca, we searched the Adverse Event Reporting System (AERS) to see if there have been any postmarketing medication error cases. Our search did not identify any medication error cases that resulted in an adverse outcome because a patient was prescribed both products. However, it is known that medication errors are under reported, thus a negative AERS search cannot guarantee that concomitant therapy has not occurred.

We also discussed the potential safety concerns of concomitant administration of Adcirca and Cialis with the medical officer from the Division of Cardiovascular and Renal Products. If a patient received the normal dose of Adcirca (40 mg daily) for arterial pulmonary hypertension and the highest dose of Cialis (20 mg) for erectile dysfunction, this would result in a total daily dose of 60 mg of tadalafil. The medical officer cited the clinical studies LVBH and LVFB, which studied doses up to 100 mg without any additional adverse events. Thus, although there is a potential for concomitant administration DCRP doesn't believe that there is a safety concern that would prohibit marketing the product with 2 different names.

Despite the lack of a safety concern that would prohibit the use of a dual proprietary name for this NDA, we are concerned that prescribers may not recognize the adverse events associated with co-administration of Adcirca with nitrates or protease inhibitors and the resultant drug:drug interactions. There has been substantial postmarketing education of prescribers, emergency personnel, and patients about the concurrent use of nitrates with sildenafil and tadalafil. The Applicant should be encouraged to educate healthcare practitioners and patients to ensure that they are aware that Adcirca and Cialis contain the same active ingredients and also have the same pharmacological profile (e.g., adverse events, drug:drug interactions, etc).

4.2 PRODUCT STRENGTH

We note the applicant has chosen to only produce a 20 mg tablet, although the recommended daily dose is 40 mg. This disparity in strength and dose introduces an unnecessary path to medication errors as patients could either take 1 tablet twice a day resulting in a sub therapeutic response or only take one tablet once daily, also resulting in a sub therapeutic response. The package insert specifically states the "dividing the dose over the course of the day is not recommended", however by offering a 20 mg tablet strength the manufacturer may inadvertently be increasing the likelihood of patients or prescribers to take only half the dose or to take it twice daily.

4.3 LABELS AND LABELING RISK ASSESSMENT

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container label appears to be vulnerable to confusion that could lead to medication errors.

The most recent label submitted by the Applicant neglects to communicate the dosage form. To ensure that healthcare practitioners can identify the product, the proposed name, established name, and dosage form should be presented on the principal display panel.

The container label neglects to warn providers that Adcirca contains the same active ingredient as Cialis. A primary concern with dual proprietary names is the likelihood of overdose or increased exposure to the same drugs without the knowledge of the patient or the practitioner. In order to avoid this the Applicant should ensure that all safeguards are utilized and that every opportunity is taken to warn practitioners that Adcirca and Cialis contain the same active ingredient. The label offers an opportunity to convey this message to practitioners in a concise statement that warns of the same active ingredients, Tadalafil. Thus, although there is a potential for concomitant administration it doesn't appear that there is a safety concern that would prohibit the use of the proprietary name, Adcirca.

5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Adcirca, is not vulnerable to name confusion from a sound and look-alike perspective that could lead to medication errors with other established and proprietary names. Additionally, DDMAC did not find the name to be promotional.

The Division of Cardio-Renal Products has concluded that a safety concern does not exist if patients were to receive concomitant administration of the maximum doses of both Cialis and Adcirca. Since there is precedence in allowing dual proprietary names for another active ingredient in this pharmacological class, Viagra and Revatio, DMEPA has not identified a safety concern that would render an objection to this proprietary name.

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.

5.1 COMMENTS TO THE DIVISION

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 Sean Bradley, Project Manager, at 301-796-1332.

5.2 COMMENTS TO THE APPLICANT

A. Proprietary Name

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

Adcirca 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 as stated in this review are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

Additionally, we recommend the following:

1. Monitor for concomitant administration of these products and the adverse events associated with the concomitant use of both marketed drug products and provide us with medication error reports regardless of adverse event.
2. Inform healthcare professionals that the same molecular entity will have two different proprietary names and ensure that providers are made aware of the issues that may arise with the introduction of this new name into the market, i.e. patients taking both medications at the same time, awareness of medications to avoid while using, etc.
3. Ensure that patients are aware that the safety concerns associated with Cialis would be the same for Adcirca and that Adcirca contains the same active ingredient as Cialis and should not be taken at the same time.
4. Ensure that the container labels and carton labeling include the statement "Same active ingredient as Cialis".

B. Product Strength

We note you have chosen to only develop a 20 mg tablet, although the recommended daily dose is 40 mg. This disparity in strength and dose introduces an unnecessary risk for medication errors as patients could either take 1 tablet twice a day resulting in a sub therapeutic response or only take one tablet once daily, also resulting in a sub therapeutic response. Additionally a prescriber might assume because it is the only dose manufactured, it is the correct dose and prescribe 20 mg instead of 40 mg. Only manufacturing the 20 mg tablet may increase diversion for unintended use with the indication of erectile dysfunction, as 20 mg is the maximum dose intended for erectile dysfunction for Cialis (Tadalafil). By producing the 40 mg tablet, this may decrease the likelihood of using Adcirca for an indication other than the approved indication of pulmonary arterial hypertension and may minimize the potential for dosing errors.

C. Labels and Labeling

1. Ensure that the label displays the proprietary name, established name and dosage form in the usual presentation, i.e. Adcirca (Tadalafil) tablets 20 mg
2. The label should contain the statement, 'Same active ingredient as Cialis', to ensure that practitioners are aware of the dual proprietary name issue and to avoid medication errors (i.e. concomitant administration) which may occur when a dual proprietary name is introduced to the market.

6 REFERENCES

1. Adverse Events Reporting System (AERS)

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

2. MICROMEDEX INTEGRATED INDEX ([HTTP://WEBLERN/](http://weblern/))

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

3. Phonetic and Orthographic Computer Analysis (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This orthographic algorithm is a database which was created for the Division of Medication Error Prevention and Analysis, 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 Error 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 and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologics, 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. US Patent and Trademarks Office (<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 DMEPA staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. We also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The DMEPA 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 DMEPA staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, we will consider the Sponsor’s intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, we also consider a variety of pronunciations that could occur in the English language.

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

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<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 Upstrokes Downstrokes	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication

		<p>Cross-strokes</p> <p>Dotted letters</p> <p>Ambiguity introduced by scripting letters</p> <p>Overlapping product characteristics</p>	
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

Inpatient Sample 1	Outpatient Sample 2	Voice
Adcirca	Adcirca	Adcirca
Adcirca	Adcirca	Adcerca
Adcirca	Adcirca	Adserca
Adcirca	Adcirca	Adserka
Adcirca	Adcira	
Adcirca	Adcirca	
	Adcirca	

Appendix C: Proprietary names discarded because they lack orthographic or phonetic similarity to the proposed name.

Proprietary Name	Similarity to Adcirca
Codeine	Look
Circanol	Look
Cialis	Look
Ciclopirox	Look
Cidex	Look
Ceclor	Look
Concerta	Look and Sound
Dynacirc	Look and sound

Appendix D: United States Patent and Trademark office name listed as “Live” form the same applicant that submitted the name Adcirca.

Proprietary Name	Similarity to Adcirca
 	Look & Sound

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Appendix E: Products with no numerical overlap in strength and dose, or excessive number of pills necessary to achieve dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Adcirca (tadalafil)		20 mg oral tablet	40 mg daily by mouth one daily
Advair (fluticasone propionate/salmeterol)	Look	Advair Diskus: 100 mcg/50 mcg 250 mcg/50 mcg 500 mcg/50 mcg Advair HFA: 45 mcg/21 mcg 115 mcg/21 mcg 230 mcg/21 mcg	Advair Diskus: Adults and children 12 years of age and older: One inhalation twice daily (morning and evening approximately 12 hours apart). Children 4 to 11 years of age: One inhalation of 100 mcg fluticasone/50 mcg salmeterol twice daily (morning and evening approximately 12 hours apart). Advair HFA: Patients 12 years of age and older: 2 inhalations twice daily (morning and evening approximately 12 hours apart).
Adacel (Pertussis, Tetanus, Diphtheria) vaccine	Sound	Injection: 2 limits of flocculation (Lf) units diphtheria toxoid, 5 Lf units tetanus toxoid, 3 mcg pertactin, 5 mcg FHA, ^b 2.5 mcg detoxified pertussis toxins, 5 mcg fimbriae types 2 and 3 per 0.5 mL	Immunization series: The primary series consists of three 0.5 mL IM doses. The customary age for the first dose is 2 months of age, but it may be given as early as 6 weeks of age and up to the seventh birthday. Preterm infants should be vaccinated according to their chronological age from birth.
Arcoxia (etoricoxib)	Look	Oral tablets: 30 mg and 60 mg	The recommended dose is 60 mg to 90 mg daily for osteoarthritis, rheumatoid arthritis, and acute gouty arthritis.
Adoxa (doxycycline tablets)	Look	Oral tablets: 75 mg, 100 mg, 150 mg.	100 mg by mouth twice daily for 7 to 60 days.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Adcirca (tadalafil)		20 mg oral tablet	40 mg daily by mouth one daily
Climara (estradiol) Transdermal, Extended-release Film	Look	Transdermal Patch: 0.025 mg/24 hour 0.0375 mg/24 hour 0.05 mg/24 hour 0.06 mg/24 hour 0.075 mg/24 hour 0.1 mg/24 hour	Treatment of vasomotor symptoms, treatment should be initiated dose at 0.025 mg/day, Climara system applied to the skin once weekly. The dose should be adjusted as necessary to control symptoms.
Alora (estradiol) Transdermal, Extended-release Film	Look	Patches: 0.025 mg/24hour 0.05 mg/24hour 0.075 mg/24hour 0.1 mg/24hour	Apply 0.025 mg per day to 0.05 mg per day transdermal system to the skin once or twice weekly.

Appendix F: Products with a single strength but multiple differentiating product characteristics

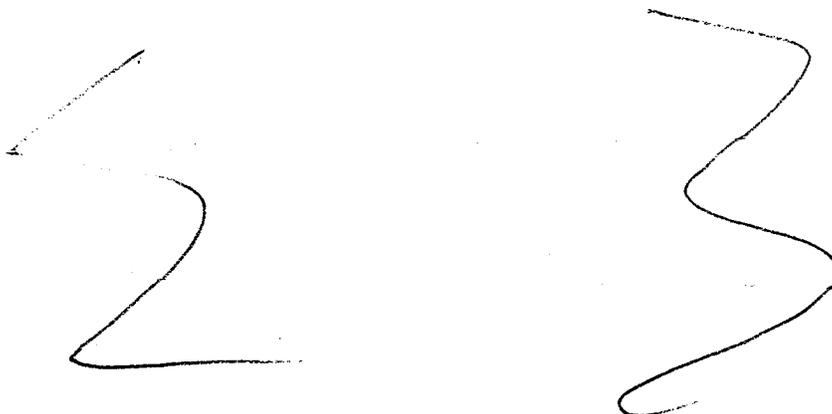
Product name with potential for confusion	Similarity to Product Name	Strength	Usual Dose (if applicable)	Other differentiating product characteristics
Adcirca (tadalafil)		20 mg oral tablet	40 mg by mouth one daily	
Aldara (Imiquimod Topical)	Look	5% topical cream	Apply 2 times per week for 16 weeks to a defined treatment area on the face or scalp (but not both concurrently). The treatment area should be one contiguous area of approximately 25 cm ² (eg, 5 cm × 5 cm).	Dosage form: tablet vs. cream Dose: 1 tablet, 2 tablet, 20 mg, or 40 mg vs. a small amount or one application Route of administration: oral vs. topical Dosing Frequency: once daily vs. twice weekly

Product name with potential for confusion	Similarity to Product Name	Strength	Usual Dose (if applicable)	Other differentiating product characteristics
Adcirca (tadalafil)		20 mg oral tablet	40 mg by mouth one daily	
Arnica (Arnica Topical)	Look	20 % Arnica Tincture	Apply locally with massage 2 or 3 times daily.	Dosage form: tablet vs. tincture Dose: 1 or 2 tablets vs. small amount Route of administration: oral vs. topical Dosing Frequency: once daily vs. two to three times daily.
Akurza (Salicylic Acid)	Sound	6% Cream	Apply a thin film of medication to the affected area, once daily at bedtime or as directed by your doctor.	Dosage form: tablet vs. cream Route of administration: oral vs. topical Dose/strength: 2 tablets vs. thin film
Adrucil (Irinotecan Injection)	Look	Injection: 50 mg/ml	12 mg/kg is given intravenously once daily for 4 successive days. The daily dose should not exceed 800 mg.	Dosage form: tablet vs. injection Prescriber: General Practitioner vs. Oncologist Dose: fixed dose, 40 mg vs. weight based regimen based on toxicity Dosing Frequency: once daily vs. Specific Chemotherapy regimen
Aclaro (Hydroquinone)	Look	Aclaro 4% emulsion, 48.2 gm bottle	Apply a small amount to an unbroken patch of skin and rub the medicine until it is evenly distributed.	Dosage form: tablet vs. emulsion Dose: 2 tablets vs. small amount Route of administration: oral vs. topical
Alinia (Nitazoxanide Oral)	Look	Oral tablets: 500 mg Powder for oral suspension: 100 mg/5 mL after reconstitution	1 to 3 years old 5 mL 4 to 11 years old 10 mL oral suspension every 12 hours with food. > 12 years old: 1 tablet or 25 mL every 12 hours with food	Frequency: once daily vs. every 12 hours Dose: 40 mg vs. 100 mg, 200 mg or 500 mg

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

Adcirca (tadalafil)	20 mg oral tablet	Usual dose: 40 mg by mouth once daily
Failure Mode: Name Confusion	Causes (could be multiple)	Effects
<p>Advicor (niacin extended-release/lovastatin tablets)</p> <p>500 mg/20 mg, 750 mg/20 mg, 1 g/20 mg, 1 g/20 mg oral extended release tablet</p> <p>One tablet orally at bedtime</p>	<p>Orthographic similarity: names share same beginning (Ad), both names have the same number of letters (seven). A dotted letter 'i' in the same area of name.</p> <p>Overlapping attainable dose and unit of measure (20 mg and 40 mg).</p> <p>Same dosage form (tablet) and route of administration (oral).</p> <p>Same frequency of administration (once daily).</p>	<p>Differing product characteristics minimize the likelihood of medication error in the usual practice setting.</p> <p><i>Rationale:</i></p> <p>Though Advicor and Adcirca share an attainable dose and unit of measure (20 mg and 40 mg), we believe that Advicor prescriptions would contain the niacin and lovastatin strengths of the product (i.e. 500/20, 750/20, 1000/20, and 1000/40), otherwise clarification would be required to differentiate between the products. We believe that this difference with Adcirca which only comes in one strength will help eliminate potential medication errors between the two products. Additionally, Advicor is recommended to be taken at bedtime, as this may help with the flushing of the niacin component, and the lovastatin component is also recommended to be taken in evening, therefore the directions will most likely be written as 'QHS'.</p>

Appendix I: Container Label



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/s/

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DRUG SAFETY OFFICE REVIEWER

Carol Holquist
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DRUG SAFETY OFFICE REVIEWER