CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-262

PROPRIETARY NAME REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 16, 2008
To:	Scott Monroe, MD, Director Division of Reproductive and Urologic Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Jinhee J. Lee, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name, Label, and Labeling Review
Drug Name:	Lo Seasonique Levonorgestrel/Ethinyl Estradiol 0.1 mg/0.02 mg Tablets Ethinyl Estradiol 0.01 mg Tablets
Application Type/Number:	NDA # 22-262
Applicant:	Duramed Pharmaceuticals, Inc.
OSE RCM #:	2008-297

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EXECUTIVE SUMMARY

The evaluation of the proposed name Lo Seasonique found some potential for confusion to occur between Lo Seasonique and Seasonique. However, the position of the prefix immediately preceding the root name may help in distinguishing Lo Seasonique from Seasonique. Our post-marketing experience has shown that modifiers placed immediately following the root name on prescription orders are often omitted or overlooked. In this case, the prefix is positioned before the root name and unattached, thus the likelihood of omission may be decreased, as evidenced in our CDER prescription studies. We further suggest that the applicant consider eliminating the space between the modifier, Lo, and the root name, Seasonique, in an effort to reduce the possibility that the two parts of the name will be separated. Moreover, attaching the modifier to the root name decreases the potential for the modifier, Lo, to be misinterpreted as a net quantity or strength, since "Lo" can resemble the number, "10". Additionally, if one were to select this medication using a computer order entry system, there is a greater potential for another oral contraceptive product using the modifier "Lo" to be selected if the modifier and root name are separated. Thus, if the applicant is requested to make these revisions, we have no objection to the use of the name.

As part of a proprietary name review, the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the blister labels, pouch, carton and insert labeling and noted that improvements could be made to decrease the potential for selection errors, to mimimize confusion with dosing, and to increase readability of information presented on the labeling. The risks DMEPA has 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.

If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. Additionally, if the product approval is delayed beyond 90 day from the date of this review, the proposed name must be resubmitted for evaluation.

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to a request from the Division of Reproductive and Urologic Products for assessment of the proprietary name "Lo Seasonique" regarding potential name confusion with other proprietary or established drug names.

1.2 REGULATORY HISTORY

Lo Seasonique is an extension of the Seasonique product line. Seasonique (NDA 21-840) was approved on May 25, 2006 for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. Lo Seasonique and Seasonique contain the same active ingredients, however, Seasonique has a greater amount of levonorgesterel/ethinyl estradiol than Lo Seasonique (i.e. 0.15 mg/0.03 mg versus 0.1 mg/0.02 mg).

1.3 PRODUCT INFORMATION

Lo Seasonique contains 84 tablets of levonorgestrel/ethinyl estradiol 0.1 mg/0.02 mg and 7 tablets of ethinyl estradiol 0.01 mg. Lo Seasonique is an oral contraceptive that lowers the risk of becoming pregnant primarily by suppressing ovulation. It is indicated for the prevention of pregnancy in women. The recommended dose is one tablet taken at the same time every day for 91 days. Lo Seasonique will be available in Extended-Regimen Tablet Dispensers each containing a 13 week supply of tablets: 84 orange tablets, each containing 0.1 mg of levonorgestrel and 0.02 mg ethinyl estradiol, and 7 yellow tablets each containing 0.01 mg of ethinyl estradiol.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by the DMEPA 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 Container Label, Carton and Insert Labeling Risk Assessment). The primary focus for both of the assessments 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, Lo Seasonique, and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, and ANDA products currently under review by the Agency.

For the proprietary name, Lo Seasonique, 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 2.1.1.1 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). DMEPA also conducts internal CDER prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.3).

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 2.1.3). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.[2] FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. 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

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

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

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.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[3]

2.1.1 Search Criteria

The 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 'Lo' 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 Lo Seasonique, the Staff also consider the orthographic appearance of the name on lined and unlined orders. We also consider the possibility that prescriptions or orders for Lo Seasonique could be misinterpreted as representing two separate products (e.g. a prescription for "Lo" and "Seasonique" written in close proximity to one another or omitted altogether). Specific attributes taken into consideration include the length of the name (12 letters), upstrokes (2, capital letters 'L', 'S'), down-strokes (one, if "q" is scripted), cross-strokes (none), and dotted letters (one, 'i'). Additionally, several letters in Lo Seasonique may be vulnerable to ambiguity when scripted, including the letter 'L' which may appear as 'C', 'F', 'T', or 'Z' and the letter 'S' may appear as 'G', 'A', or 'L'; lower case 'a' appear as a lower case 'o' or 'u'; and '-que' may appear as '-gue'. As such, the Staff should also consider these alternate appearances when identifying drug names that may look similar to Lo Seasonique.

When searching to identify potential names that may sound similar to Lo Seasonique, the medication error staff search for names with similar number of syllables (4), stresses (LO-sea-son-ique or lo-SEA-son-ique or lo-sea-SON-ique or lo-sea-son-ique), consonant sound pronunciation ('q' versus 'g'), and placement of vowel and consonant sounds. We searched for the pronunciation of the root name, Seasonique, in the present insert labeling, but could not find it. Thus, 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.

The Staff also consider 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

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[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)

were provided with the following information about the proposed product: the proposed proprietary name (Lo Seasonique), the established name (levonorgestrel/ethinyl estradiol and ethinyl estradiol), proposed indication (prevention of pregnancy in women), strength (01. mg/0.02 mg and 0.01 mg, dose (1 tablet), frequency of administration (daily), route (oral) and dosage form of the product (tablet). Appendix A provides a more detailed listing of the product characteristics the nedication error staff general take into consideration.

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, Lo Seasonique, was provided to the medication error staff of the 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 Lo Seasonique using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 6. 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 DMEPA to gather CDER professional opinions on the safety of the product and the proprietary name, Lo Seasonique. 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.

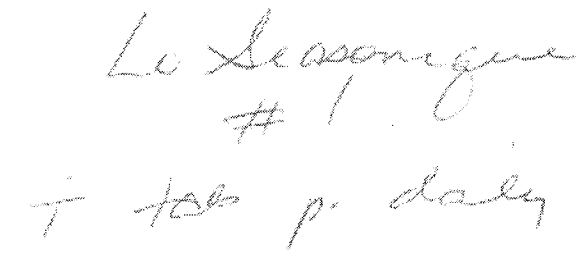
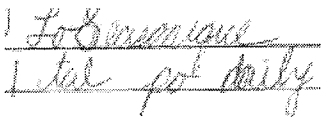
2.1.2 CDER Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Lo Seasonique 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 124 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 Lo Seasonique 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 124

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. Lo Seasonique Study (conducted on March 25, 2008)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
Outpatient Prescription: 	Lo Seasonique #1 1 tablet by mouth daily.
Inpatient Medication Order : 	

2.1.3 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 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, DMEPA seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective then remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies

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

potential failure modes by asking: "Is the name Lo Seasonique 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 Lo Seasonique 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 posses 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.

DMEPA will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. 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 and another drug product.

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

If none of these conditions are met, then DMEPA will not object to the use of the proprietary name. If any of these conditions are met, then DMEPA will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the

safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the 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, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Applicant, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Applicant'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, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

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

2.2 LABEL AND LABELING RISK ASSESSMENT

This section describes the methods and materials used by the DMEPA Staff to conduct a label, labeling, and/or packaging risk assessment (see Section 3, Results). The primary focus of the assessments is to identify and remedy potential sources of medication errors 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. [7]

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 label 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 United States Pharmacopeia-Institute for Safe

[7] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[8]

Because the DMEPA staff analyzes reported misuse of drugs, the DMEPA staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. DMEPA 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.

DMEPA reviewed the following labels and labeling submitted by the Applicant on February 28, 2008. See Appendices G through I for pictures of the labels and labeling.

- Blister Labels (Commercial Product and Professional Sample)
- Pouch Labels (Commercial Product and Professional Sample)
- Carton Labeling (Commercial Product)
- Package Insert Labeling (no image)

2.3 ADVERSE EVENT REPORTING SYSTEM (AERS) SEARCH

Since the root name "Seasonique" is currently marketed, we conducted a search of the Adverse Event Reporting System (AERS) database to identify any medication errors associated with the use of Seasonique. 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", "Pharmaceutical Product Complaint", and verbatim substance name "Seasoniq%", tradename "Seasoniq%" were used as search criteria on July 7, 2008. Additionally, we conducted a search using the "Drug Interaction" function to see whether there was specific confusion between Seasonique and Seasonale.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Databases and information sources

In total, twelve names were identified as having some similarity to the name Lo Seasonique.

Seven of the twelve names were thought to look like Lo Seasonique, which include: Fosinopril, Loperamide, Lo-Ovral, Lactulose, Sulfasalazine, Fosfomycin, and Low-Ogestrel. Leucine was thought to sound like Lo Seasonique. Four names (Seasonique, Seasonale Lo, Seasonale, and Lo-Seasonale***) were thought to look and sound similar to Lo Seasonique.

As of July 7, 2008, the proposed name, Lo Seasonique, did not contain a U.S. Adopted Name (USAN) stem.

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

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

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the DMEPA staff (see section 3.1.1. above) and recommended looking at previous drug name reviews that included the name "Lo" in the prefix.

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 30 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. About two thirds of the participants (n=18) interpreted the name correctly as "Lo Seasonique," with all of the outpatient written study participants and 88% of the inpatient written study participants interpreting the proposed name correctly. The misinterpretations occurred in the phonetic prescription study with the prefix in Lo Seasonique reported mainly as 'La-', 'Li', or 'Le' instead of 'Lo-' and the prefix of the 2nd part of the name interpreted as 'ce-' or 'si', instead of 'sea-'. One participant misinterpreted 'Lo' as 'Ro'. In the written prescription studies, the prefix of the second word of the name was misinterpreted as 'Sec-'. Many of the participants added a hyphen or did not separate 'Lo' from 'Seasonique'. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Independent searches by the primary Safety Evaluator did not identify any additional names thought to look and/or sound similar to Lo Seasonique and represent a potential source of drug name confusion. Careful attention was afforded to drug names beginning with the letters 'Lo' but no additional drug names beginning with these letters was thought to have the potential for confusion with Lo Seasonique. As such, a total of twelve names were analyzed to determine if the drug names could be confused with Lo Seasonique 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 Lo Seasonique, and thus determined to present some risk for confusion. Failure modes and effects analysis was then applied to determine if the proposed name, Lo Seasonique, could potentially be confused with any of the twelve names and lead to medication error. Eight of the names lacked orthographic and phonetic similarity (Appendix C).

The analysis of three of the four remaining names revealed that these three names were unlikely to result in medication errors for reasons described/outlined in Appendices D and E.

The FMEA determined that Seasonique was vulnerable to confusion and medication errors due to the similarity between this already existing product and its product line extension, Lo Seasonique (see Appendix F). However, the analysis determined that placing the modifier "Lo" in front of the root name, Seasonique, may minimize the potential for confusion and subsequent error. Moreover, our analysis found that deleting the space between Lo and Seasonique may further reduce the potential for confusion because it may lessen the chance that the modifier and root name will be separated.

3.2 LABEL AND LABELING RISK ASSESSMENT

Our analysis of the labels and labeling determined the following areas of vulnerability.

3.2.1 General Comments

The established name and strength appears less prominent than some of the other statements present on the labels and labeling.

The established name is not at least ½ the size of the proprietary name in accordance to 21 CFR 201.10(g)(2).

The word 'and' is present in the established name.

The term "extended-regimen" appears on the labels and labeling to describe the 91-day tablet regimen. Also, we note the words "Extended-Regimen" appear prominently on the labels and labeling.

3.2.2 Blister Labels (Commercial Product and Professional Sample)

See General Comments in section 3.2.1.

The sample blister label appears identical to the commercial blister label.

The blister labels for months 1 and 2 do not have statements indicating the week, while the blister label for month 3 does indicate the week.

The statement "Sample not for sale" does not appear prominently on the label.

3.3 ADVERSE EVENT REPORTING SYSTEM (AERS) SEARCH

Our AERS search retrieved one medication error case involving confusion between Seasonale and Seasonique. The reporter expressed concern about the name similarity and was suggesting that this name pair be added to the "name alert" list. The case was reported in 2006 and cited that look-alike and sound-alike names may lead to confusion and error.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

Introduction of a new product into an established product line is often a source of confusion. Errors introduced by dual tradename or product line extensions are multi-factorial in nature and can stem from the similarity of product names, overlapping product characteristics coupled with the low level of awareness or knowledge of the product profile by healthcare professionals and patients. With respect to the nomenclature, Lo Seasonique will be added to an existing product line, Seasonique, which has the same established ingredient and product characteristics. The only deviation of the two products lies in the strength; Seasonique has a greater amount of levonorgesterel/ethinyl estradiol than the proposed product, Lo Seasonique (i.e. 0.15 mg/0.03 mg versus 0.1 mg/0.02 mg).

In our assessment, we note that the position of the prefix immediately preceding the root name may help in distinguishing Lo Seasonique from Seasonique. Our post-marketing experience has shown that modifiers placed immediately following the root name on prescription orders are often omitted or overlooked. However, it appears that when the prefix is positioned before the root name, the likelihood of omission may be decreased, as evidenced in our post-marketing surveillance. We further suggest that the applicant consider eliminating the space between the modifier, Lo, and the root name, Seasonique, in an effort to reduce the possibility that the two parts of the name will be separated. Moreover, attaching the modifier to the root name decreases the potential for the modifier, Lo, to be misinterpreted as a net

quantity or strength, since "Lo" can resemble the number, "10". Additionally, if one were to select this medication using a computer order entry system, there is a greater potential for another oral contraceptive product using the modifier "Lo" to be selected if the modifier and root name are separated. Therefore, we would want to see the space deleted to help minimize the possibility of this type of confirmation error.

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 once the product is commercially marketed. However, DMEPA believes that these limitations are sufficiently minimized by the use of an Expert Panel, the CDER Prescription Studies that involved 124 CDER practitioners, and, in this case, the data submitted by the Applicant from an independent proprietary name risk assessment firm, which included the responses of frontline practitioners.

4.2 LABEL AND LABELING RISK ASSESSMENT

Our Label and Labeling Risk Assessment noted that both the established name and the strength appeared less prominent than some of the other statements present on the labels and labeling. The headings for the days of the week as well as the statement describing the tablet dispenser (i.e. Extended Regimen) appear more prominent. The proprietary and established names, as well as the strength, should be the most prominent statements on the labels and labeling and readily identifiable.

The term "Extended-Regimen" is vague and appears to imply that this dosing schedule provides additional benefit over other oral contraceptive tablets or dosing schedules since the word "extended" is defined in Merriam-Webster's Online dictionary as "drawn out in length especially of time". The term "extended" is used to describe the "extended-release" formulations, which allow for a reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form. Also, the "Extended-Regimen" statement is in bold font on the pouch label and a white color block distinguishes this statement from the words, "Tablet Dispensers", on the carton labeling. These words appear to be more prominent in both instances and thus bringing more weight and prominence to the words, "Extended Regimen". Consequently, we have concerns that a patient using this drug product may mistakenly believe that each tablet has a longer effect than another oral contraceptive product.

We also note the word 'and' is present in the established name. This implies that all tablets in the product are a combination of ethinyl estradiol and levonorgestrel/ethinyl estradiol. We reviewed other labels (i.e. Seasonique) and these products do not use the word 'and' in the established name.

We note that the blister labels for month 3 indicate the week with each row beginning with week 9 whereas months 1 and 2 do not. Not including the respective weeks on months 1 and 2 labels would introduce confusion because the regimen spans 13 weeks. Thus, month 1 should begin with week 1 and month 2 with week 5 for this to be used as a reminder tool. Otherwise, the days of the week for months 1 and 2 are meaningless.

The "Sample not for sale" statement appears in small font on the right corner of the blister and pouch labels. It is difficult to differentiate the sample tablet dispensers from the commercial ones. The distinction should be obvious and clear.

5 CONCLUSIONS AND RECOMMENDATIONS

Our analysis of the propose proprietary name indicates that the proposed name may be confused with Seasonique if the "Lo" portion of the name is omitted or overlooked in the prescribing or dispensing phases of the medication use system. However, we do not object to the use of the name, Lo Seasonique, because the risk of omission may be minimized prior to approval. We recommend that the Applicant consider revising the name by eliminating the space between the modifier and the root name. Additionally, DDMAC does not object to the proposed name, Lo Seasonique, from a promotional perspective.

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

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed blister and pouch labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, DMEPA notes problems with the prominence, presentation, and consistency of information on the labels and 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.

5.1 COMMENTS TO THE DIVISION

DMEPA would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy DMEPA on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Cherye Milburn, project manager, at 301-796-0567.

5.2 COMMENTS TO THE APPLICANT

5.2.1 Proprietary Name

DMEPA has no objections to the use of the proprietary name Lo Seasonique for this product. However, the position of the prefix immediately preceding the root name may help in distinguishing Lo Seasonique from Seasonique. Our post-marketing experience has shown that modifiers placed immediately following the root name on prescription orders are often omitted or overlooked. In this case, the prefix is positioned before the root name and unattached, thus the likelihood of omission may be decreased, as evidenced in our CDER prescription studies. We further suggest that the applicant consider eliminating the space between the modifier, Lo, and the root name, Seasonique, in an effort to reduce the possibility that the two parts of the name will be separated. Moreover, attaching the modifier to the root name decreases the potential for the modifier, Lo, to be misinterpreted as a net quantity or strength, since "Lo" can resemble the number, "10". Additionally, if one were to select this medication using a computer order entry system, there is a greater potential for another oral contraceptive product using the modifier "Lo" to be selected if the modifier and root name are separated.

If **any** of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. If the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

5.2.2 Labels and Labeling

1. Increase the prominence of the established name so that it is at least ½ the size of the proprietary name as required by 21 CFR 201.10(g)(2).
2. The product strength appears small in comparison to the proprietary name. The strength along with the established and proprietary names should be the most prominent information displayed on the principal display panel. Thus, we request you increase the size of the strength.
3. Delete the word 'and' in the established name. This word implies that all tablets in teh product are a combination of ethinyl estradiol and levonorgestrel/ethinyl estradiol. Present the established name as follows:

   Levonorgestrel/Ethinyl Estradiol 0.1 mg/0.02 mg tablets

   Ethinyl Estradiol 0.01 mg tablets
4. The term "Extended-Regimen" is ambiguous and its intended meaning may be misinterpreted (e.g. extended-release tablets) and thus misleading. We recommend removal of this term from the labels and labeling to avoid the potential for misinterpretation.
5. Ensure a lot number and expiration date is on the labels and labeling.
6. Include the respective week statements (e.g. week 1, week 2, etc.) for each row on the month 1 and 2 blister labels.
7. Increase the font size of the "Sample not for sale" statement so that it is clearly differentiated from the commercial tablet dispensers.

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 manufacturers that have approved products in the U.S. The main utility of a 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://csi.micromedex.com)*

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

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

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

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

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

6. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

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

7. ***Drugs@FDA*** *(http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)*

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

8. ***Electronic online version of the FDA Orange Book*** *(http://www.fda.gov/cder/ob/default.htm)*

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

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

Provides information regarding patent and trademarks.

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

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

11. ***Data provided by Thomson & Thomson's SAEGIS ™Online Service, available at*** *(www.thomson-thomson.com)*

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

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

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

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

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

14. ***USAN Stems*** *(http://www.ama-assn.org/ama/pub/category/4782.html)*

List contains all the recognized USAN stems.

15. ***Red Book Pharmacy's Fundamental Reference***

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

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

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

17. ***Medical Abbreviations Book***

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The medication error staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The medication error staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The medication error staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the medication error staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, DMEPA will consider the Applicant's intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, DMEPA also considers a variety of pronunciations that could occur in the English language.

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

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstokes Downstrokes Cross-stokes	• Names may look similar when scripted, and lead to drug name confusion in written communication

		Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B:

CDER Prescription Study Responses

Inpatient Prescription	Voice Prescription	Outpatient Medication Order
LoSeasonique	Loseasonique	Lo Seasonique
LoSeasonique	Laseasonique	Lo Seasonique
LoSecuonique	Lacizanic	Lo Seasonique
LoSeasonique	Locephinique	Lo Seasonique
LoSeasonique	Lo-Seasonique	Lo Seasonique
LoSeasonique	Loceseneke	Lo Seasonique
LoSecisonique	La Seasonique	Lo Seasonique
Lo-Seasonique	LoSeasonique	Lo Seasonique
	Liseasonique	Lo Seasonique
	Losidnique	
	Le Seasonique	
	Loseasonique	
	Rosiznik	

Appendix C: Names that lack convincing orthographic and/or phonetic similarities

Name	Similarity to Lo Seasonique
Fosinopril	Look
Loperamide	Look
Lo-Ovral	Look
Lactulose	Look
Sulfasalzine	Look
Fosfomycin	Look
Low-Ogestrel	Look
Leucine	Look and Sound

Appendix D: Products whose proposed proprietary names were found unacceptable and/or withdrawn.

Name	Similarity to Lo Seasonique	Status
Seasonale Lo***	Look and Sound	Unacceptable (OSE 05-271, January 30, 2006)
Lo Seasonale***	Look and Sound	Application withdrawn as of April 6, 2006.

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

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

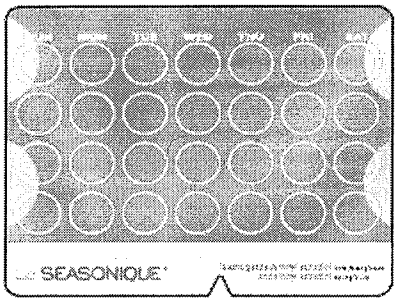
Lo Seasonique® (Levonorgestrel/Ethinyl Estradiol and Ethinyl Estradiol)	**0.1 mg/0.02 mg and 0.01 mg**	**Usual dose: 1 tablet taken at the same time every day for 91 days.**
Failure Mode: Name confusion	**Causes (could be multiple)**	**Effects**
Seasonale	Orthographic and phonetic similarity (Both of the root names contain "Season-" and have a similar number of letters (nine versus ten). With the exception of the modifier "Lo" which appears at the beginning of the root name, the names have three syllables. Both share the same indication for use (prevention of pregnancy in women, patient and prescriber population, usual dose (1 tablet), route of administration (oral), dosage form (tablet), frequency of administration (once daily) and storage location in the pharmacy. Moreover, 84 of the tablets have the identical active ingredient (levonorgestrel/ethinyl estradiol).	Orthographic and phonetic differences in the names minimize the likelihood of medication error in the usual practice setting. *Rationale:* The risk for medication error is minimized by the orthographic and phonetic differences in the names. Lo Seasonique is preceded by the letters "Lo" which help to differentiate Seasonale from Lo Seasonique because this addition results in a longer orthographic appearance and adds an additional syllable to the pronunciation of the name. Additionally, Lo Seasonique has a downstroke letter, "q", at the end of the name, while Seasonale has an upstroke letter, "l". The sounds of the suffixes also help to differentiate the names since they sound distinct when pronounced ("-AL" versus "-EEK"). Furthermore, our post-marketing surveillance did not provide any evidence for the name pair, Seasonale and Sesonique, to be a concern. There was one case citing that these names should be added to a "name alert" list, however, no actual or potential cases were identified. Adding a modifier to the beginning of the name, Seasonique, will further differentiate the two names from one another. Thus, we believe the potential for confusion is minimal.

Appendix F: Name found to have some risk of error

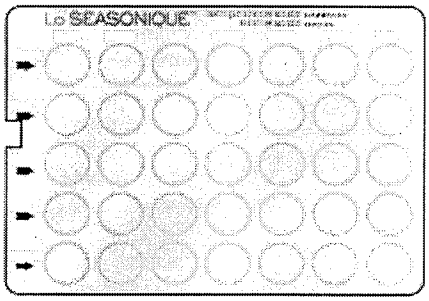
Lo Seasonique® (Levonorgestrel/Ethinyl Estradiol and Ethinyl Estradiol)	**0.1 mg/0.02 mg and 0.01 mg**	**Usual dose: 1 tablet taken at the same time every day for 91 days.**
Failure Mode: Name confusion	**Causes (could be multiple)**	**Effects**
Seasonique	Orthographic and phonetic similarity (Both names share the root name "Seasonique"). With the exception of the modifier "Lo" which appears at the beginning of the root name, the names are identical. Both share the same indication for use (prevention of pregnancy in women, patient and prescriber population, usual dose (1 tablet), route of administration (oral), dosage form (tablet), frequency of administration (once daily) and storage location in the pharmacy. Moreover, both have the same established name (levonorgestrel/ethinyl estradiol and ethinyl estradiol).	Orthographic and phonetic differences in the names minimize the likelihood of medication error in the usual practice setting. *Rationale:* The risk for medication error is minimized by the orthographic and phonetic differences in the names. Lo Seasonique is preceded by the letters "Lo" which help to differentiate Seasonique from Lo Seasonique because this addition results in a longer orthographic appearance and adds an additional syllable to the pronunciation of the name. However, we believe there is some risk of error because the modifier and root name are detached and separated by a space. The modifier, "Lo", can be mistaken as the number, 10, and in turn misinterpreted as a quantity or strength. Additionally, if one were to select this medication using a computer order entry system, there is a greater potential for another oral contraceptive product using the modifier "Lo" to be selected if the modifier and root name are separated. Thus, we believe that the space between the modifier and the root name should be eliminated.

Appendix G: Blister Labels (Commercial Product and Professional Sample)

Month 1 & 2

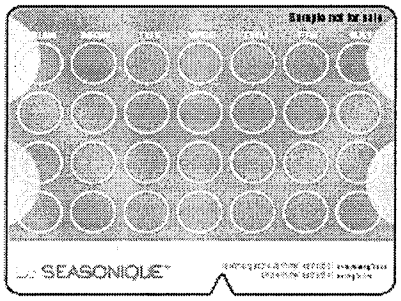


Month 3

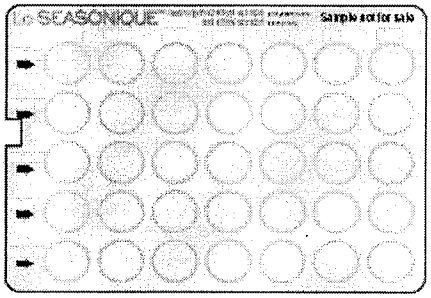


Orange circles do not print.
Indicate tablet placement.

Month 1 & 2

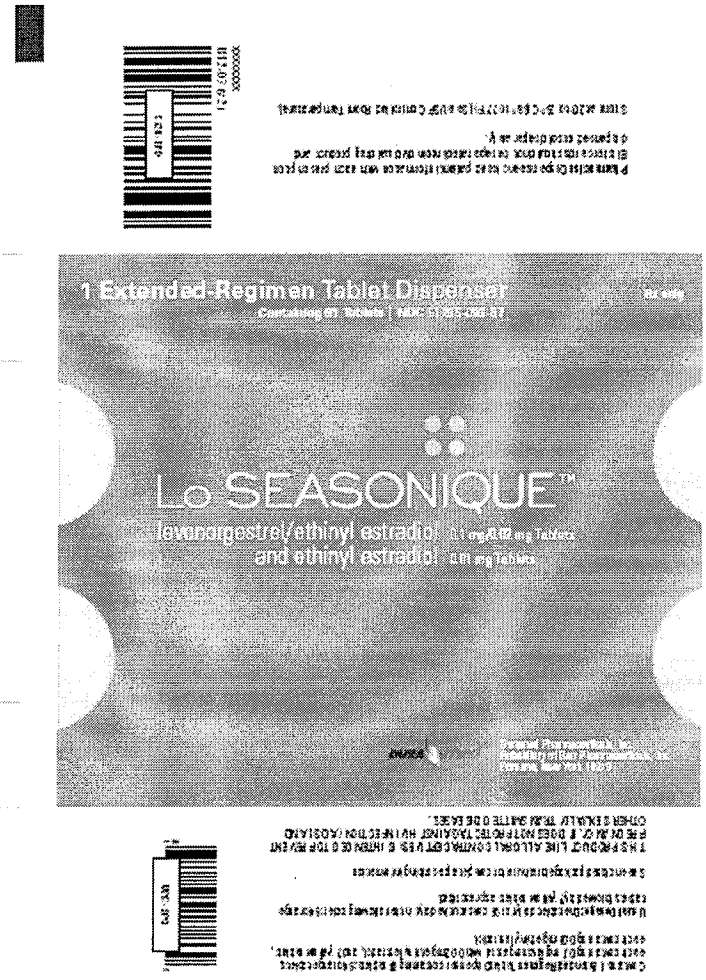


Month 3



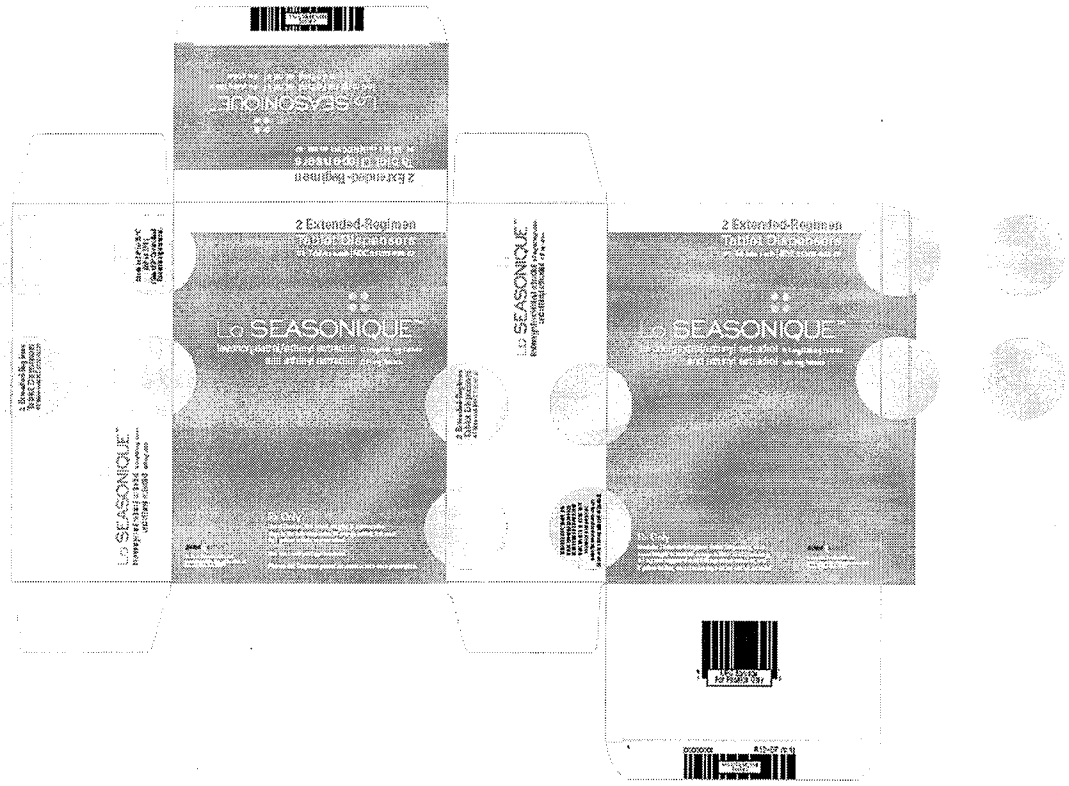
Orange circles do not print.
Indicate tablet placement.

Appendix H: Foil Pouch (Commercial Product and Professional Sample)



1 Extended-Regimen Tablet Dispenser
Rx only
Sample not for sale
Lo SEASONIQUE™
levonorgestrel/ethinyl estradiol
and ethinyl estradiol

Appendix I: Carton Labeling (Commercial Product)



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