CENTER FOR DRUG EVALUATION AND RESEARCH

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PROPRIETARY NAME REVIEW(S)

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Date:	April 7, 2008
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From:	Kristina C. Arnwine, PharmD, Acting Team Leader Division of Medication Error Prevention
Subject:	Proprietary Name, Label and Labeling Review
Drug Name(s):	Aplenzin (Bupropion HBr) Extended-release Tablets 174 mg, 348 mg, 522 mg
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EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Aplenzin, has some similarity to other proprietary and established drug names, but the findings of the FMEA indicates that Aplenzin does not appear to be vulnerable to name confusion that could lead to medication errors from a sound-alike/look-alike perspective. Thus, we have no objection to the use of the name, Aplenzin, for this product. However, we are concerned about concomitant use of Aplenzin and other bupropion containing products such as Wellbutrin and Zyban. These concerns can be minimized with labeling revisions and an educational campaign.

The results of the Label and Labeling Risk Assessment find the proposed container labels and insert labeling introduce vulnerabilities that could lead to medication errors. These potential errors can be minimized prior to approval. The Division of Medication Error Prevention's recommendations for label and labeling modifications are found in Section 5.2.

1 BACKGROUND

This review was written in response to a request from the Division of Psychiatry Products for assessment of the proprietary name, Aplenzin, regarding potential name confusion with other proprietary or established names. Container labels and insert labeling were also submitted and reviewed from a medication error perspective.

1.1 REGULATORY HISTORY

The applicant initially submitted the proposed proprietary name [redacted]. The Division of Medication Error Prevention had safety concerns about the proposed name and these concerns were discussed with the review division on June 6, 2007. The applicant withdrew the name. Subsequently, the applicant submitted the proposed proprietary names [redacted] and Aplenzin (alternate). The Division of Drug Marketing, Advertising, and Communication (DDMAC) found the name [redacted] unacceptable from a promotional perspective and the review Division concurred with DDMAC in an email dated July 24, 2007. Thus, we did not conduct a safety review for [redacted] and are only reviewing Aplenzin from a safety perspective.

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1.2 PRODUCT INFORMATION

Aplenzin (bupropion hydrobromide extended-release tablets) is an aminoketone antidepressant indicated for the treatment of major depressive disorder. The usual dose of Aplenzin is 348 mg by mouth per day, titrated up from 174 mg per day. Aplenzin is supplied in 174 mg, 348 mg and 522 mg tablets in bottles of 30 tablets and 90 tablets. The Aplenzin 174 mg tablet is equivalent to 150 mg of bupropion hydrochloride, the Aplenzin 348 mg tablet is equivalent to 300 mg bupropion hydrochloride, and Aplenzin 522 mg tablet is equivalent to 450 mg of bupropion hydrochloride.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by the medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Container, Carton Label, and Insert Label Risk Assessment). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. 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. [1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Aplenzin, 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 Aplenzin, the medication error staff 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 hold an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.5). We also conduct internal 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. We use the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the Staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

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, 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]

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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.

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

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 'S' 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 Aplenzin the Staff also consider the other orthographic appearance of the names on lined and unlined orders. Specific attributes taken into consideration of Aplenzin include length of the name (8 letters), upstrokes (two upstrokes, capital letter 'A' and letter 'l'), downstrokes (two downstrokes, letters 'p' and 'z'), and dotted letters (one dotted letter, letter 'i'). Additionally, several letters in Aplenzin, may be vulnerable to ambiguity when scripted, including the letter 'A' may appear as 'Cl', 'Ci', 'Ce'; lower case 'p' appear as a lower case 'q'; lower case 'l' may appear as lower case 't', 'b', 'd' or 'e'; lower case 'e' may appear as lower case 'i', 'a', 'o', or 'l'; lower case 'n' may appear as lower case 'm', 'r', 's', or 'u'; lower case 'z' may appear as a lower case 'g', 's', or 'x'; and lower case 'i' may appear as a lower case 'e' or 'i'. As such, the Staff also considered these alternate appearances when identifying drug names that may look similar to Aplenzin.

When searching to identify potential names that may sound similar to Aplenzin the Medication Error Staff searched for names with similar number of syllables (4), stresses (A-plen-zin, a-PLEN-zin, or a-plen-ZIN), and placement of vowel and consonant sounds. 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.

2.1.1.1 Data base and information sources

The proposed proprietary name, Aplenzin, was provided to the medication error staff 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 Aplenzin using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the Medication Error Staff 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 the medication error staff to gather CDER professional opinions on the safety of the product and the proprietary name Aplenzin. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of Medication Error Prevention Staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

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[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. Artifical Inteligence in Medicine (2005)

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

Figure 1. Aplenzin Study (conducted on July 27, 2007)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
Outpatient Prescription: Aplenzin 174 mg Disp #60 Take 1 tablet by mouth daily	Aplenzin, 174 mg dispense 60 take one tablet by mouth daily.
Inpatient Medication Order: aplenzin 174mg 1 tab po daily	

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, we seek 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 also considers whether or not the use of dual tradenames can be a source of error within the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug names. 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 potential failure modes by asking: "Is the name Aplenzin 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 Aplenzin 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.

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

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

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. We identify that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug another drug product.

In the event that 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 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, 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 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, 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 Applicant 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 error of the currently proposed name, and so we 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

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 medication error staff analyzes reported misuse of drugs, the staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use 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 27, 2006 the following labels and insert labeling for us to review (see Appendices G and H):

- Container Label: 174 mg and 348 mg, 30 tablets and 90 tablets (Appendix G)

Additionally, on April 26, 2007, the Applicant submitted the following labels:

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- Container Label : 522 mg, 30 tablets and 90 tablets (Appendix G)

Moreover, on June 28, 2007, the Applicant submitted the following :

- Insert Labeling (no image)

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Data base and information sources

In total, eight products were identified as having some similarity to the name Aplenzin.

Five of the eight names were thought to look similar to Aplenzin: Apresoline, Aplenar, Plendil, Apilepsin, and Cephalexin.

One name, Asendin, was thought to sound similar to Aplenzin.

Two names, Aplidin and Aplindin, were thought to sound and look similar to Aplenzin.

The proposed name did not contain any U.S. Adopted Name (USAN) stems.

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

3.1.2 CDER Expert panel discussion

The Expert Panel reviewed the pool of names identified by the medication error staff (see section 3.1.1. above), and no additional names were thought to have orthographic similarity to Aplenzin. DDMAC found the proposed name acceptable from a promotional perspective.

3.1.3 Prescription analysis studies

A total of 34 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. About 71% of the participants (n=24) interpreted the name correctly as "Aplenzin" with correct interpretation occurring more frequently in the written studies. The remainder of the participants misinterpreted the drug name. The majority of misinterpretations occurred in the outpatient prescription study, with the letter 'A' reported as 'Al', the letter 'z' reported as the letter 's', and the second letter 'n' reported as 'a' and 'u'. In the outpatient written study the letter 'z' was reported as the letter 'e' and the second letter 'n' was reported as the letter 'm'. In the verbal prescription study, the letter 'i' was reported as the letter 'e' by two respondents, the second letter 'n' was reported as the letter 'd' by one respondent, and there was a letter 'e' appended to the end of the proposed name by one respondent. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 Safety evaluator risk assessment

Independent searches by the primary Safety Evaluator did not identify any additional names thought to look or sound similar to Aplenzin.

As such, a total of eight names were analyzed to determine if the drug names could be confused with Aplenzin and if the drug name confusion would likely result in a medication error. This analysis determined that the name similarity between Aplenzin and the identified names was unlikely to result in medication errors for all eight products.

One name, Aplidin, is —— used to treat multiple myeloma and acute lymphoblastic leukemia. No additional information about the product could be found in commonly used drug references such as Facts and Comparisons, Clinical Pharmacology, Micromedex, and the Orange Book. No information could be found on one name, Aplindin, which was most likely a misspelling of the aforementioned name, Aplidin. One name, Aplenar, is a name trademarked by a Finnish corporation for a pharmaceutical product, and the final name, Apilepsin, is valproate sodium, marketed in Russia. b(4)

For three of the names (Apresoline, Plendil, and Asendin), FMEA determined that medication errors were unlikely because the products do not overlap in strength or dosage with Aplenzin and have minimal orthographic and/or phonetic similarity to the proposed products (Appendix E).

The remaining name (Cephalexin) had increased orthographic similarity to the proposed product; however it did not have numerical overlap with Aplenzin in either dosage or strength. Analysis of the failure mode did not determine the effect of this similarity to result in medication errors in the usual practice setting (Appendix F).

We also noted this product contains bupropion, the same active moiety in Wellbutrin and Zyban products, and their generic equivalents, yet it utilizes a different proprietary name. This product is also marketed by the same sponsor that markets Zyban and the Wellbutrin product line.

3.2 LABEL AND LABELING RISK ASSESSMENT

Review of the container labels and insert labeling identified several potential sources of medication errors.

3.2.1 Container Label

The net quantity is presented in close proximity to the product strength

The "Warning" statement lacks appropriate prominence.

The "Dosage" statement is misleading.

There is no banner advising practitioners of the different salt.

3.2.2 Insert Labeling

The Dosage and Administration section, "Switching Patients from Wellbutrin, Wellbutrin SR, or Wellbutrin XL" sub-section does not include specific information on switching patients from Wellbutrin XL to Aplenzin.

The Dosage and Administration section does not include information regarding switching from the Wellbutrin product line to Aplenzin if the patient is currently taking a daily dose other than 150 mg, 300 mg, or 450 mg of bupropion hydrochloride (e.g. 200 mg twice daily or 75 mg three times daily).

The Dosage and Administration section does not include information advising pharmacy staff not to substitute Aplenzin for Wellbutrin, or vice versa, at the pharmacy level.

4 DISCUSSION

4.1 PROPRIETARY NAME, LABEL AND LABELING RISK ASSESSMENT

The results of the Proprietary Name Risk Assessment found that the proposed name, Aplenzin, has some similarity to other proprietary and established drug names, but the findings of the FMEA indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors from a look and/or sound-alike perspective. However, there is a strong likelihood for Aplenzin to be confused with other bupropion containing products and the Wellbutrin and Zyban product lines.

The proposed product, Aplenzin, contains the same active moiety as the Wellbutrin product line (bupropion). However, Aplenzin contains the hydrobromide salt, while the Wellbutrin product line contains the hydrochloride salt. This overlap in active moiety represents a potential source for error in the medication use process. For example, if the proposed product is ordered by the established name, bupropion hydrobromide, there is a potential for the salt to be overlooked or omitted from the prescription, resulting in misinterpretation and dispensing as the incorrect product. The fact that the salt contained in each product begins with "hydro-" and end with "-ide" may contribute to confirmation bias as the presence of orthographically similar salts on a prescription order may lead practitioners to believe that "bupropion hydrochloride" has been prescribed instead of "bupropion hydrobromide" and vice versa. Therefore, despite the inclusion of the salt in the prescription order, the incorrect product may still be dispensed. However, the sponsor has formulated the hydrobromide product with product strengths that are non-overlapping and not numerically similar to the hydrochloride products (174 mg, 348 mg, and 522 mg vs. 75 mg, 100 mg, 150 mg, 200 mg, and 300 mg). At a minimum, if an order for bupropion hydrobromide is misinterpreted as bupropion hydrochloride, the inclusion of the product strength on the prescription order should elicit a call to the prescriber. Additionally, the strengths of the hydrobromide product are not achievable by the currently marketed strengths of Wellbutrin and Zyban. Thus, if misinterpreted you could not halve or double the hydrochloride strengths to achieve the dose prescribed.

Despite these differences in product strength, the use of a tradename also represents a potential source for error because there is a possibility for co-prescribing this medication. This product was originally proposed to be marketed as , which in our opinion is more confusing than marketing the product under an entirely different name. Whether marketing this product under or a different tradename, there is still a risk of concomitant administration. As evidenced by errors seen with Zyban and Wellbutrin, concomitant dosing may occur because patients and healthcare practitioners will be unaware that Zyban and Wellbutrin contain the same active moiety as Aplenzin. The concern was communicated to the review Division in a meeting on June 6, 2007. We questioned why this product needed to be marketed and if there was a benefit to the formulation, given the potential confusion that already exists within the bupropion product lines. However, the Division determined there was no regulatory reason to prevent the approval of this application. Given this decision, the Division of Medication Error Prevention believes marketing the product under a different name with non-achievable doses is a better alternative to using the name because no modifier could adequately convey the differences in product salts. If marketed under there is also a strong likelihood that the modifier might be omitted or misinterpreted or that healthcare practitioners may think the hydrobromide product was just a different strength of the currently marketed product. We recognize using a different proprietary name to communicate the different salt may pose a risk for concomitant administration with the Wellbutrin product line and other buproprion containing products; however it is our opinion that these product differences in salt and strength may be better communicated to health care professionals under a different name. Thus, in addition to utilizing a different proprietary name, educational efforts are essential to minimize these risks.

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Our analysis of the container label and insert labeling identified other areas of concern that may contribute to the confusion between Aplenzin and the Wellbutrin product line. A sub-section in the Dosage and Administration section is titled "Switching Patients from Wellbutrin, Wellbutrin SR, or Wellbutrin XL"; however this sub-section does not include specific dosing information regarding switching patients from Wellbutrin XL to Aplenzin. Even though the dosing regimen is the same (once daily) for both Wellbutrin XL and Aplenzin, this information should be included as well or prescribers will not know how to convert patients from Wellbutrin XL to Aplenzin. Moreover, this sub-section does not provide instructions for switching patients from all available strengths/daily doses of Wellbutrin. A lack of information regarding conversion of patients on a Wellbutrin product with a daily dose other than 150 mg, 300 mg, or 450 mg could lead to dosing errors as prescribers may not know how to convert patients from the Wellbutrin product line to Aplenzin.

We noted the Dosage and Administration section also does not contain information with regard to not substituting Aplenzin for Wellbutrin, and vice versa, at the pharmacy level. Without this information, pharmacists and/or pharmacy technicians may believe that Aplenzin can be substituted for Wellbutrin, Zyban, or their generic equivalents at the pharmacy level without instruction from the prescriber to do so. This may lead to dosing errors due to improper substitution which could subsequently result in adverse events.

Our analysis of the container labels noted that the net quantity is presented in close proximity to the product strength on the container label. Postmarketing experience demonstrates that presentation of the net quantity in close proximity to the product strength may lead to confusion of one value for another. The risk of confusion would be minimized if these numbers appeared in different locations on the label. We also noted the "Dosage" statement on the container label is misleading. As currently presented, the portion of the statement implies that this medication can be taken more than once daily. Taking this medication more than once daily may cause the patient to take more than the maximum daily dose of 522 mg, which greatly increases the potential for seizures. Additionally, we noted that the lacks appropriate prominence and may be overlooked. If patients overlook this warning, they will not be aware that this product is not to be taken with other

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products that contain bupropion, which may lead to patients exceeding the maximum daily dose of bupropion, thereby increasing the potential for seizures. Moreover, we noted the container label does not contain a banner informing practitioners of the different salt, hydrobromide. Without this banner, practitioners may overlook the salt in the established name, and dispense this product as the hydrochloride salt in error.

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

5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Aplenzin, does not appear to be vulnerable to name confusion that could lead to medication errors from a look and sound-alike perspective. As such, we have no objections to the use of the proprietary name, Aplenzin, for this product. However, it should be noted that there is still a risk of concomitant administration of this product in combination with other Wellbutrin, Zyban, or bupropion containing products. Practitioners need to be made fully aware of the differences in the salt, proper conversion, and non-interchangeability of these products. If **any** of the proposed product characteristics as stated in this review are altered prior to approval of the product; we rescind this Risk Assessment finding, and 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.

Based upon our assessment of the container labels and carton and insert labeling we have identified areas of needed improvement, listed in section 5.2 below. We believe the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

We have no objection to the use of the proprietary name, Aplenzin, for this product. However, we are concerned there is still a risk of concomitant administration between Aplenzin and other bupropion containing products such as Wellbutrin, Zyban, and their generic equivalents. If any of the proposed product characteristics as stated in this review are altered prior to approval of the product; we rescind this Risk Assessment finding, and 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.

Based upon our assessment of the proprietary name, labels and labeling, we have identified areas needed of improvement. We have provided recommendations in Section 5.2 and request this information be forwarded to the Applicant.

We would appreciate feedback on the final outcome of this review. Please copy us on any communication to the Applicant with regard to this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Daniel Brounstein, Project Manager, at 301-796-0674.

5.2 COMMENTS TO THE APPLICANT

A. Proprietary Name

Our analysis indicated having a separate tradename for this product poses less of a risk of confusion than naming the product . Thus we have no objection to the use of the name, Aplenzin, for this product. b(4)

However, there is still a risk of concomitant administration between Aplenzin and other bupropion containing products such as Wellbutrin, Zyban, and their generic equivalents because patients and healthcare practitioners will not be aware that the products contain the same active moiety.

If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommends that the name be resubmitted for review.

B. Container Label

1. Relocate the net quantity so that it is not presented in close proximity to the product strength.
2. Revise the "Dosage" statement to .
3. Increase the prominence of the "WARNING by highlighting the warning or using a different color text. b(4)
4. Include a "Different Salt" banner on the principal display panel not to exceed six months.

C. Package Insert Labeling

1. Include an example conversion regarding switching patients from Wellbutrin XL to Aplenzin in the "Switching Patients from Wellbutrin, Wellbutrin SR, or Wellbutrin XL" sub-section of the Dosage and Administration section.
2. Include instructions on switching patients from a Wellbutrin product to Aplenzin if their daily Wellbutrin dose does not currently equal 150 mg, 300 mg, or 450 mg.

7. 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 a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing 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/)

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, FDA.

4. 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.

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 Error Prevention

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

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 and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, 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. WWW location http://www.uspto.gov.

Provides information regarding patent and trademarks.

10. 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.

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 tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. 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.

13. 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.

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.pharmacist.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. 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 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, we 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, 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	• 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 Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication

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

Appendix B:

CDER Prescription Study Responses for Salonpas Arthritis Pain

Inpatient Written	Outpatient Written	Verbal
Alplenzia	Aplenein	Aplenzen
Aplensiu	Aplenzim	Aplenzen
Aplenzia	Aplenzin	Aplenzid
Aplenzin	Aplenzin	aplenzin
Aplenzin	Aplenzin	Aplenzin
Aplenzin	Aplenzin	Aplenzine
Aplenzin	Aplenzin	
Aplenzin	Aplenzin	
Aplenzin	Aplenzin	
Aplenzin	Aplenzin	
Aplenziu	Aplenzin	
	Aplenzin	
	Aplenzin	
	Aplenzin	
	Aplenzin	
	Aplenzin	
	Aplenzin	

Appendix C: Identified product name that was likely a misspelling of another identified product name

Proprietary Name	Similarity to Aplenzin
Aplindin	Look

Appears This Way
On Original

Appendix D: Identified product name(s) with little or no product information.

Proprietary Name	Similarity to Aplenzin
Aplidin	Look

Appendix E: Proprietary names used only in Foreign Countries

Proprietary Name	Similarity to Aplenzin	Country
Aplenar	Look	Finland
Apilepsin	Look	Russia

Appendix F: Products with no numerical overlap in strength and dose

Aplenzin		174 mg, 348 mg, 522 mg	Usual dose: One tablet by mouth once daily
Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Apresoline	Look	Tablets: 10 mg, 25 mg, 50 mg, 100 mg Injection: 20 mg/mL	Severe essential hypertension (Injection): 20 mg to 40 mg repeated as necessary Essential hypertension: 10 mg to 50 mg by mouth four times daily
Plendil	Look	2.5 mg, 5 mg, 10 mg	Hypertension: 2.5 mg to 10 mg by mouth once daily
Asendin	Sound	25 mg, 50 mg, 100 mg, 150 mg	Depression: 200 mg to 400 mg by mouth once daily or in divided doses

Appears This Way
On Original

Appendix G: Potential confusing name without numerical overlap in strength or dose, but with increased look-alike similarity

Aplenzin	174 mg, 348 mg, 522 mg	Usual dose: One tablet by mouth once daily
Failure Mode: Name confusion	Causes (could be multiple)	Effects
Cephalexin Tablets: 250 mg Capsules: 250 mg, 500 mg Powder for Oral Suspension: 125 mg/5 mL, 250 mg/5 mL	Orthographic similarity: 'Apl' vs. 'Ceph', 'zin' vs. 'xin' Aplenzin  Cephalexin 	The necessity of a product strength when prescribing Aplenzin or Cephalexin decreases the potential for name confusion between these two products. *Rationale:* Both products are available in multiple strengths. The inclusion of a desired strength on a prescription order will differentiate Aplenzin from Cephalexin since the product strengths for each product differ from one another numerically, and are not similar in sound or look (e.g. 174 mg does not sound like 250 mg when pronounced or look similar when scripted).

2 Page(s) Withheld

_____ Trade Secret / Confidential

2 Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Proprietary Name Review*____

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/s/

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