CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-421

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:	February 5, 2010
To:	Russell Katz, MD, Director Division of Neurology Products
Through:	Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis
From:	Carlos M Mena-Grillasca, RPh, Team Leader Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name(s):	Mirapex ER (Pramipexole Dihydrochloride) Extended-release Tablets 0.375 mg, 0.75 mg, 1.5 mg, 3 mg, 4.5 mg
Application Type/Number:	NDA 022421
Applicant:	Boehringer Ingelheim
OSE RCM #:	2010-311

1 INTRODUCTION

This review is written in response to the anticipated approval of this NDA within 90 days from the date of this review. DMEPA found the proposed name, Mirapex ER, acceptable in OSE Reviews #2009-116 and 2009-116-1, dated April 14, 2009 and August 14, 2009, respectively. Since those reviews, none of Mirapex ER's product characteristics have been altered. Additionally, on January 30, 2009 DDMAC reviewed the proposed name and had no concerns regarding the proposed name from a promotional perspective. Furthermore, the review Division did not have any concerns with the proposed name, Mirapex ER during our initial review.

2 METHODS AND RESULTS

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources (see section 4) to identify names with orthographic and phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name reviews. We used the same search criteria used in OSE Review #2009-116 and 2009-116-1 for the proposed proprietary name, Mirapex ER. Since none of the proposed product characteristics were altered we did not re-evaluate previous names of concern.

Additionally, DMEPA searches the United States Adopted Names (USAN) stem list to determine if the name contains any USAN stems as of the last USAN updates. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proposed proprietary name, and focuses on the avoidance of medication errors.

The searches of the databases did not yield any new names thought to look or sound similar to Mirapex ER and represent a potential source of drug name confusion.

DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of February 3, 2010.

3 CONCLUSIONS AND RECOMMENDATIONS

The re-review of Mirapex ER did not identify any additional names thought to look or sound similar to the proposed name since our last review. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Mirapex ER, for this product at this time.

DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Neurology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

4 REFERENCES

1. OSE reviews # 2009-116 and 2009-116-1, dated April 14, 2009 and August 14, 2009, respectively. Proprietary Name Review of Mirapex ER; Toombs, L. Shenee'

2. 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.

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

USAN Stems List contains all the recognized USAN stems.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22421	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	PRAMIPEXOLE DIHYDROCHLORIDE

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/s/

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02/05/2010

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02/05/2010

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

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Date:	August 14, 2009
To:	Russell Katz, MD, Director Division of Neurology Products
Through:	Carlos M Mena-Grillasca, RPh, Acting Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	L. Shenee' Toombs, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
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Application Type/Number:	NDA 22-421
Applicant:	Boehringer Ingelheim
OSE RCM #:	2009-116

CONTENTS

1 INTRODUCTION

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Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of August 14, 2009.

3 CONCLUSIONS AND RECOMMENDATIONS

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DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Neurology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

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

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

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

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08/14/2009

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08/14/2009

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:	April 14, 2009
To:	Russell Katz, MD, Director Division of Neurology Products
Thru:	Carlos M Mena-Grillasca, RPh, Acting Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
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Application Type/Number:	NDA 22-421
Applicant:	Boehringer Ingelheim
OSE RCM #:	2009-116

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CONTENTS

EXECUTIVE SUMMARY

Our analysis of the proposed proprietary name Mirapex ER indicates that confusion can occur between Mirapex and Mirapex ER. Although this finding would lead to DMEPA objecting to the proposed name our FMEA determined the use of an alternate proprietary name can lead to concomitant therapy with Mirapex and the alternate name. The Applicant's proposal to add a modifier to the Mirapex root name is a recognized naming convention commonly used when an extended release dosage form is added to a product line with an existing immediate-release product. Therefore, we will not object to the use of the name, Mirapex ER, for this product. However, we recommend at the time of product launch the Applicant inform healthcare practitioners about the differences between Mirapex ER and currently marketed Mirapex products. Further enhancements to the labels and labeling will also minimize the confusion between Mirapex and Mirapex ER.

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to a request from the Applicant, Boehringer Ingelheim, on January 15, 2009, for a review of the proposed proprietary name, Mirapex ER. The Applicant also submitted container labels and carton labeling for review, which will be reviewed under separate cover (OSE Review #2009-119).

1.2 PRODUCT INFORMATION

Mirapex ER (Pramipexole Dihydrochloride) is an extended-release tablet indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease. The recommended starting dose is 0.375 mg given once per day. Based on efficacy and tolerability, dosages may be increased gradually but not more frequently than every five to seven days, first to 0.75 mg per day and then by 0.75 mg increments up to a maximum recommended dose of 4.5 mg per day. Mirapex ER is supplied as 0.375 mg, 0.75 mg, 1.5 mg, 3 mg, and 4.5 mg extended-release tablets in 30-count unit of use bottles.

Mirapex, approved July 1, 1997, is available as immediate-release tablets in 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.25 mg, and 1.5 mg strengths. Mirapex is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease and restless leg syndrome.

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis conducting a proprietary name risk assessment (see section 2.1). The primary focus for the assessment is to identify and remedy potential sources of medication errors prior to drug approval. The Division of Medication Error Prevention and Analysis 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]

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 08/08/2008.

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Mirapex ER, and the proprietary and established names of drug products existing in the marketplace and those products with pending IND, NDA, BLA, and ANDA currently under review by CDER.

For the proprietary name, Mirapex ER, DMEPA searched a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see 2.1.1) and held a CDER Expert Panel Discussion (EPD) to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). We also conduct internal FDA prescription analysis studies (see 2.1.2), and when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment. DMEPA also evaluated the appropriateness of the proposed modifier/suffix, and considered the potential for modifier/suffix's omission or misinterpretation, and verified that the modifier/suffix did not appear on the error-prone abbreviation list maintained by the Institute of Safe Medication Practices (ISMP). Additionally, the suffix/modifier was assessed for resemblance to any numbers, dosing instructions, or medical abbreviations and evaluation for the potential for the suffix/modifier to be confusing or misleading was taken into consideration.

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 2.1.4). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.[1] FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. We use the clinical expertise of DMEPA 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, DMEPA considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics 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.[2]

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

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

2.1.1 Search Criteria

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

For this review, particular consideration was given to drug names beginning with the letter 'M' 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.[1,1]

To identify drug names that may look similar to Mirapex ER, DMEPA also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (9 letters), upstrokes (three, capital letters 'M', 'E', 'R'), down strokes (one, lower case letter 'p'), cross-strokes (one, lower case letter 'x'), and dotted letters (one, lower case 'i'). Additionally, several letters in Mirapex may be vulnerable to ambiguity when scripted, including the capital letter 'M' may appear as 'N', 'Z', or 'B'; lower case 'i' may resemble a lower case 'j' or 'e' ; lower case 'r' may appear as lower case 'n', 'v', or 'u'; lower case 'a' may appear as lower case 'e', 'o', or 'c'; lower case 'p' may appear as lower case 'y', 'g', 'f', 'j', 'q' or 'z'; lower case 'e' may resemble a lower case 'a','o', or 'c'; and lower case 'x' may resemble a lower case 'r', 't', 'f', or 'k'. As such, DMEPA also considers these alternate appearances when identifying drug names that may look similar to Mirapex ER.

When searching to identify potential names that may sound similar to Mirapex, DMEPA searches for names with similar number of syllables (5), stresses (MIR-a-pex "E R"; mir-A-pex "E R"; mir-a-PEX "E R"), and placement of vowel and consonant sounds. In addition, several letters in Mirapex ER may be subject to interpretation when spoken; including the letters 'Mir' may be interpreted as 'Mer', the letter 'a' may be interpreted as 'o', the letters 'pex' may be interpreted as 'peks'. The Sponsor's intended pronunciation of the proprietary name was also taken into consideration (MIR-ah-pex), as it was included in the Proprietary Name Review Request submitted by the Applicant on January 15, 2009.

DMEPA also considers the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting For this review, DMEPA was provided with the following information about the proposed product: the proposed proprietary name (Mirapex ER), the established name (Pramipexole Dihydrochloride), proposed indication (treatment of the signs and symptoms of idiopathic Parkinson's disease), strength (0.375 mg, 0.75 mg, 1.5 mg, 3 mg, 4.5 mg), dose (0.375 mg to 4.5 mg), frequency of administration (once daily), route of administration (oral) and dosage form of the product (tablet). Appendix A provides a more detailed listing of the product characteristics DMEPA generally takes into consideration.

Lastly, DMEPA also considers the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names 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 DMEPA provides additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and Information Sources

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

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

description of the databases used in the searches is provided in Section 6. To complement the process, DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 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, Mirapex ER. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of Division of Medication Error Prevention and Analysis (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed.

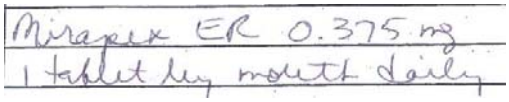
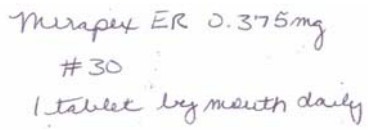
The pooled results of DMEPA are presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice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

2.1.2 FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Mirapex ER 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 Mirapex ER in handwriting and verbal communication of the name, one inpatient and one outpatient medication order was 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 DMEPA.

Figure 1. Mirapex ER Study 0130 (conducted on January 30, 2009)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Medication Order:  	Mirapex ER 0.375 mg Dispense 30 One tablet by mouth daily
Outpatient Medication Order:  	

2.1.3 FDA Adverse Event Reporting System (AERS) Database

Since the root name Mirapex has been marketed since 1997, DMEPA conducted a search of the Adverse Event Reporting System (AERS) database to determine if there are any medication errors associated with the currently marketed Mirapex product which may be indicative of potential confusion with Mirapex ER. For this review, the timeframe used for the AERS search was May 1, 2006 to February 27, 2009 because an AERS search had previously been conducted during a label/labeling review of Mirapex (OSE Review 06-113).

The MedDRA Higher Level Group Term (HLGT) Medication Error, the Preferred Term (PT) Pharmaceutical Product Complaint (PPC), verbatim substance names "Mirap%" and Pramipex%, tradename "Mirapex", and active ingredient "Pramipexole" were used as search criteria.

The cases were manually reviewed to determine if medication errors occurred. Those cases that did not describe a medication error were excluded from further analysis. For cases describing a medication error, we reviewed the cases to identify factors that contributed to the errors, and to ascertain if these risks might apply to the proposed Mirapex ER.

2.1.4 Comments from the OND review Division or Generic drugs

DMEPA requests the regulatory division in the Office of New Drugs responsible for the application for their comments or concerns with the proposed proprietary name and any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. Any comments or concerns are addressed in the safety evaluator's assessment.

The regulatory division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys the decision to accept or reject the name. The regulatory division is requested to concur/not concur with DMEPA's final decision.

2.1.5 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[1] 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 than remedies available in the post-approval phase.

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

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Mirapex ER 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 Mirapex ER 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 possesses 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 a proposed proprietary name when one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].

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

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. DMEPA identifies a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

In the event that 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 of the name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

If none of these criteria are met, then DMEPA will not object to the use of the proprietary name. If any of these criteria 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 Sponsor; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the IOM, WHO, JCAHO, and ISMP, which 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 Sponsor, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after a Sponsor has 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. In that instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

The search retrieved eighteen names as having some similarity to Mirapex ER.

Fifteen of the eighteen names were thought to look like Mirapex ER. These include: Merapur HP, Meruvax, (b) (4), Methampex, Mifeprex, Miradon, Miragran, Miralax, Miranax, Mirap, Miraphen LA, Miraphen PE, Miraxil, Norflex, and Zenapex. Three names (b) (4), Mirapex, Mirazep) were thought to look and sound similar to Mirapex ER.

When evaluating the appropriateness of the modifier, DMEPA noted ten drug products (Depakote ER, Dynahist ER, Flagyl ER, Metadate ER, Methylin ER, Opana ER, Razadyne ER, Trituss ER, Ultram ER and Vospire ER) listed in the Orange Book and/or Drugs@FDA containing the modifier 'ER' in their proprietary names. The modifier is utilized to distinguish the immediate-release formulation from the extended-release formulation.

The frequency of administration for Trituss ER, Vospire ER, and Opana ER is twice daily. Although the specific dosing for Dynahist ER is unavailable, based on the ingredients in the product, Dynahist ER is likely dosed twice daily, whereas the frequency of administration for the remaining products is once daily. The frequency of administration for these currently marketed drug products using the modifier "ER" denotes either a once or twice daily dosing interval. Therefore, the use of the modifier, "ER", to signify the extended-release formulation of Mirapex dosed once daily, adheres with the dosing interval of other extended-release formulations currently on the market.

The proposed proprietary name, Mirapex ER, does not contain a USAN stem as of the last date searched, January 30, 2009.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by Division of Medication Error Prevention and Analysis (see section 3.1.1), and noted no additional names thought to have orthographic or phonetic similarity to Mirapex ER.

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

3.1.3 FDA Prescription Analysis Studies

A total of 23 responses were evaluated in the prescription analysis studies. Ninety-one percent of the participants (n=21) interpreted the name correctly as "Mirapex ER". The remaining responses misinterpreted the drug name as "Merapex ER", both in the outpatient prescription. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 FDA Adverse Event Reporting System (AERS) Database

On May 9, 2006, DMEPA conducted an AERS search to identify medication errors related to Mirapex as part of a labeling review (OSE Review 06-113). A total of eleven pertinent medication error reports were retrieved during that analysis.

Of the eleven cases, DMEPA identified ten medication error cases involving name confusion with the proprietary name "Mirapex". These cases were associated with the following products: Miralax (n=6), Minipress (n=2), Mykrox (n=1) and Mifeprex (n=1). The remaining case expressed concern that "All bottles of all strengths look exactly alike except the # of dose."

In total, three names from the 2006 AERS search results were added to this proprietary name assessment: Minipress, Mykrox, and Minipress XL (included because it is a line extension of Minipress and uses a modifier). The names Miralax and Mifeprex were already identified during the database searches.

For this review, the AERS search performed to identify any additional medication errors related to Mirapex from May 1, 2006 until February 27, 2009 did not identify any relevant cases.

3.1.5 Comments from the Division of Neurology Products

In response to the OSE January 30, 2009 e-mail, the Division of Neurology Products did not forward any comments and or concerns on the proposed proprietary name at the initial phase of the name review.

DMEPA notified the Division of Neurology Products via e-mail that we had no objections to the proposed proprietary name; Mirapex ER, on March 10, 2009. Per e-mail correspondence from the Division of Neurology Products on March 24, 2009, they indicated they concur with our assessment of the proposed proprietary name, Mirapex ER.

3.1.6 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator identified eight additional names: seven thought to look similar to Mirapex ER (Berifen, Binafex, Binafin, Binopen, Merapril, Mirpan and Winpar), and one (Mirapexin), which was thought to look and sound similar to Mirapex ER. These names are thought to represent a potential source of drug name confusion. One name (b) (4) could not be identified as a drug name or product and will not be reviewed further. As such, a total of 28 names were analyzed to determine if the drug names could be confused with Mirapex ER and if the drug name confusion would likely result in a medication error.

One name was not analyzed further as the names lack convincing orthographic and/or phonetic similarity (see Appendix C).

The remaining twenty-seven names identified were determined to have some orthographic and/or phonetic similarity to Mirapex ER, and thus determined to present some risk for confusion. Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name, Mirapex ER, could potentially be confused with any of the twenty-seven names and lead to medication errors in clinical practice.

This analysis determined that the name similarity between Mirapex ER and the identified names was unlikely to result in medication errors for the twenty-six products. See Appendices D through G for our evaluation of the twenty-six products identified.

The remaining name, Mirapex, was determined to be vulnerable to confusion due to orthographic and phonetic similarities with the proposed name Mirapex ER as discussed in section 4.

4 DISCUSSION

Mirapex ER will be added to an existing product line that already has an immediate-release oral dosage formulation. The Applicant proposes to use the root name Mirapex and the modifier ER to differentiate the extended-release formulation from the currently marketed product Mirapex. This naming convention is commonly used when an extended-release dosage form is added to a product line with an existing immediate-release formulation.

Post-marketing experience has shown that the introduction of product line extensions, result in medication errors if the modifier is omitted and product characteristics are similar or overlap. In this instance both formulations of Mirapex and Mirapex ER have overlapping product characteristics (see Appendix H). By choosing to develop an extended-release formulation of pramipexole tablets with product characteristics that overlap with those of the currently marketed pramipexole immediate-release tablets, the Applicant

has eliminated a potentially valuable error-reduction strategy that has been employed in other product line extensions. If, the Applicant chose a product strength with a small deviation from the 0.75 mg and 1.5 mg immediate-release Mirapex strengths, the differences in strength would offer an opportunity for an error to be caught before it reaches the patient, if the modifier were omitted or overlooked. However, since the Applicant has completed their clinical trials and submitted their new drug application, DMEPA acknowledges it is unlikely that the product strength will be changed at this time.

In conducting the FMEA, we identified failure modes including omission of the Mirapex ER modifier. If the ER modifier is omitted from orders of Mirapex ER 0.75 mg or 1.5 mg, it is almost certain that Mirapex (immediate-release tablets) will be dispensed since Mirapex has overlapping 0.75 mg and 1.5 mg strengths with Mirapex ER.

DMEPA also analyzed the approach of using an alternative proprietary name for the Pramipexole extended-release product while maintaining the Mirapex name for the immediate release product. This FMEA identified the additional failure mode of concomitant therapy, which was not identified in the FMEA for the proprietary name, Mirapex ER.

Since there is precedent using this naming convention and the modifier "ER" denotes a frequency of administration of once or twice daily, Mirapex ER is an acceptable proprietary name for extended-release pramipexole dihydrochloride. However, because practitioners may not recognize the dosing frequency differences between Mirapex and Mirapex ER, DMEPA recommends that the Applicant alert practitioners and patients on the proper use of this product and clearly communicate the available strengths for both products.

5 CONCLUSIONS & RECOMMENDATIONS

Our analysis of the proposed proprietary name Mirapex ER indicates that confusion can occur between Mirapex and Mirapex ER. Although this finding would lead to DMEPA objecting to the proposed name our FMEA determined the use of an alternate proprietary name can lead to concomitant therapy with Mirapex and the alternate name. The Applicant's proposal to add a modifier to the Mirapex root name is a recognized naming convention commonly used when an extended-release dosage form is added to a product line with an existing immediate-release product. Therefore, we do not object to the use of the name, Mirapex ER, for this product. However, we recommend at the time of product launch the Applicant inform healthcare practitioners about the differences between Mirapex ER and currently marketed Mirapex products, and clearly communicate the available strengths for both products. Further enhancements to the labels and labeling will also minimize the confusion between Mirapex and Mirapex ER.

5.1 COMMENTS TO THE DIVISION

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Daniel Brounstein, OSE project manager, at 301-796-0674.

5.2 COMMENTS TO THE APPLICANT

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

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

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

We recommend at the time of product launch you inform healthcare practitioners about the differences between Mirapex ER and currently marketed Mirapex product, and clearly communicate the available strengths for both products.

REFERENCES

1. Micromedex Integrated Index (http://csi.micromedex.com)

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

2. Phonetic and Orthographic Computer Analysis (POCA)

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

3. 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.

4. AMF Decision Support System [DSS]

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

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

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

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

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

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

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

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

Provides information regarding patent and trademarks.

9. 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.

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

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

11. 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.

12. 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.

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

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

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

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

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

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

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

		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 Medication Order	Outpatient Medication Order	Voice Prescription
Mirapex ER	Mirapex ER	Mirapex ER
Mirapex ER	Mirapex ER	Mirapex ER
Mirapex ER	Mirapex ER	Mirapex ER
Mirapex ER	Mirapex ER	
Mirapex ER	Mirapex ER	
Mirapex ER	Mirapex ER	
	Mirapex ER	
	Mirapex ER	
	Merapex ER	
	Merapex ER	
	Mirapex ER	
	Mirapex ER	
	Mirapex ER	
	Mirapex ER	

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

Proprietary Name	Similarity to Mirapex ER
Methampex	Look

Appendix D: Proprietary names that are internationally registered

Proprietary Name	Similarity to Mirapex ER	Active Ingredient	Country
Merapril	Look	Captopril	Italy
Merapur HP	Look	Menotrophin	Mexico
Miragran	Look	Naratriptan	Chile
Miranax	Look	Naproxen	Sweden, Austria, Finland
Mirap	Look	Mirtazapine	Ireland
Mirapexin	Look and Sound	Pramipexole	Belgium, Czech Republic, Denmark, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Spain, United Kingdom
Mirazep	Look and Sound	Mirtazapine	India, Phillipines
Mirpan	Look	Maprotoline	Denmark
Miraxil	Look	Proparacaine	Colombia
Binafex	Look	Terbinafine	Mexico
Binafin	Look	Terbinafine	Russia
Binopen	Look	Ampicillin	Brazil
Berifen	Look	Diclofenac	Indonesia
Winpar	Look	Cinnarizine	Mexico

Appendix E: Discontinued products with no generic equivalent available

Proprietary Name	Similarity to Mirapex ER	Established Name
Miradon	Look	Anisindione
Miraphen LA	Look	Guaifenesin/Phenylpropanolamine
Miraphen PE	Look	Guaifenesin/Phenylephrine
Minipress XL	Look	Prazosin

Appendix F: Discontinued products with generics available under another proprietary name more likely to be used on a prescription (identified in AERS Search)

Proprietary Name	Similarity to Mirapex ER	Proprietary name likely to be used
Mykrox	Look	Zaroxolyn

Appendix G: Products with no numerical overlap in strength and usual dose

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Mirapex ER (Pramipexole) extended-release tablet		**0.375 mg, 0.75 mg, 1.5 mg, 3 mg, 4.5 mg**	*Starting Dose:* 0.375 mg given once per day. *Maintenance Dose*: 0.75 mg - 4.5 mg once per day
Norflex (Orphenadrine)	Look	Injection: 30 mg/mL	Administer 60 mg IV or IM; May be repeated every 12 hours
(b) (4)			
Zenapax (Daclizumab)	Look	Injection: 25 mg/5 mL	Administer 1 mg/kg IV over a 15 min. period for five doses. First dose given prior to transplant. Remaining 4 doses given at intervals of 14 days.
Minipress (Prazosin)	Look	Capsule: 1 mg, 2 mg, 5 mg	Take 1 mg-20 mg per day in divided doses.
Miralax (Polyethylene Glycol Solution)	Look	Powder for Solution: 119 gm, 238 gm, 510 gm containers.	One heaping dose (17 gm) of powder per day in 8 ounces of water.
Mifeprex (Mifepristone)	Look	200 mg Tablet	Take 600 mg single oral dose
Meruvax II (Rubella Virus Vaccine, Live)	Look	Powder for Injection: >/= 1000 tissue culture infectious doses (TCID) of rubella per 0.5 mL dose.	Administer 0.5 mL subcutaneous in the outer aspect of the upper arm

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

Appendix H: Mirapex and Mirapex ER Overlapping Product Characteristics

	Mirapex	Mirapex ER
Established name	Pramipexole	Pramipexole
Indication	• Treatment of signs and symptoms of Parkinson's disease (three times daily) • Restless leg syndrome (once daily)	• Treatment of signs and symptoms of Parkinson's disease (once daily) • Not applicable
Route of Administration	Oral	Oral
Strength	0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg	0.375 mg, 0.75 mg, 1.5 mg, 3 mg, 4.5 mg
Dose	• 0.375 mg- 4.5 mg/day • 0.125 mg-0.5 mg (before bedtime)	• 0.375 mg- 4.5 mg/day • Not applicable
Total daily dose	4.5 mg	4.5 mg
Frequency	three times daily	once daily
Dosage Form	tablet (Immediate-release)	tablet (Extended-release)

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