CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-436

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:	April 24, 2009
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From:	Anne Crandall, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name and Label Review for Lipsovir
Drug Name:	Lipsovir (Acyclovir and Hydrocortisone Cream, 5%/1%)
Application Type/Number:	NDA 22-436
Applicant:	Medivir
OSE RCM #:	2008-1862

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

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EXECUTIVE SUMMARY

Our evaluation has concluded that the proposed name, Lipsovir, is unacceptable because it contains the United States Adopted Name (USAN) stem '-vir'. This stem is used by USAN to indicate an antiviral drug. Although Lipsovir is a proposed antiviral product and its use is consistent with the intended USAN meaning, the USAN Council uses this stem for established names only. The use of stems in proprietary names can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the chance of confusion among those drugs which may compromise patient safety. Additionally, the USAN definition of the stem '-vir' is antiviral, although this does define one of the ingredients in Lipsovir, it does not reflect the other active ingredient, Hydrocortisone.

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

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Antiviral Products to evaluate the proposed proprietary name for its potential to contribute to medication errors. The proprietary name, Lipsovir, is evaluated to determine if the name could be potentially confused with other proprietary or established drug names. Additionally, labels and labeling were submitted for risk assessment and overall evaluation for product information and clarity.

1.2 REGULATORY HISTORY

The NDA was submitted September 30, 2008. The sponsor submitted the name Lipsovir for review on October 9, 2008.

1.3 PRODUCT INFORMATION

Lipsovir contains the active ingredients Acyclovir and Hydrocortisone, both currently marketed creams, in one formulation for the treatment of early signs and symptoms of recurrent herpes labialis to prevent the redevelopment and reduce the duration of ulcerative cold sores in adults and adolescents (12 years of age and older). The usual dose is a thin film applied to cover affected area including the outer margin. The product will be available as a cream containing 5% Acyclovir and 1% Hydrocortisone in 2 gram and 5 gram tubes.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling and/or package risk assessment (see 2.2 Container and Insert Label Risk Assessment). The primary focus for this assessment is to identify and remedy potential sources of medication error prior to drug approval. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.[1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

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

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.6). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.[1] FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. We define a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [2] We use the clinical expertise of 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 of the proposed name may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

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

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

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

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

2.1.1 Search Criteria

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

For this review, particular consideration was given to drug names beginning with the letter 'L' 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 Lipsovir, DMEPA also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (eight letters), upstrokes (one, capital letter 'L'), downstrokes (one, 'p'), cross-strokes (none), and dotted letters (two, 'i'). Additionally, several letters in Lipsovir may be vulnerable to ambiguity when scripted, including the letter 'L' which may appear similar to 'U', 'Z', 'h', or 'I'; the letter 'i' may appear as 'e'; lower case 'p' may appear as a lower case 'g' or 'j'; lower case 's' may appear as a lower case 'n', 'v' or 'r'; lower case 'o' may appear as 'a' or 'e'; lower case 'v' may appear as 'n', 'u', 'r' or 's'; lower case 'r' may appear as a lower case 'n', 'v', 'u', or 's' As such, DMEPA also considers these alternate appearances when identifying drug names that may look similar to Lipsovir.

When searching to identify potential names that may sound similar Lipsovir, DMEPA searches for names with similar number of syllables (three), stresses (LIP-so-vir, lip-SO-vir or lip-so-VIR), and placement of vowel and consonant sounds. In addition, several letters in Lipsovir may be subject to interpretation when spoken, including the letter 'i' may be interpreted as 'e'; 'p' may be interpreted as 'b'; the letters 's' may be interpreted as 'z', and 'vir' as 'veer'. As such, DMEPA also considers these alternate pronunciations when identifying drug names that may sound similar to Lipsovir. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

DMEPA also considers the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, DMEPA were provided with the following information about the proposed product: the proposed proprietary name (Lipsovir), the established name (Acyclovir and Hydrocortisone), proposed indication (treatment of signs and symptoms of recurrent herpes labialis), strength (5%/1%, respectively), dose (thin film to affected area), frequency of administration (five times daily), route of administration (topical) and dosage form of the product (cream).

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

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

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

Appendix A provides a more detailed listing of the product characteristics that the medication error staff typically take 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 (or components of the proprietary name) can be a source of error in a variety of ways.

As such, these broader safety implications of the name are considered and evaluated throughout this assessment and DMEPA provides additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.2 Database and Information Sources

The proposed proprietary name, Lipsovir, 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 Lipsovir using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Appendix A. 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.

2.1.3 CDER Expert Panel Discussion

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

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

2.1.4 FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Lipsovir 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 Lipsovir in handwriting and verbal communication of the name, inpatient medication orders are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one prescription is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating

health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA.

Figure 1. Lipsovir Study 1203 (conducted on Decemeber 3, 2008)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
Inptatient Written Prescription: ~~Lipsovir~~ ~~Apply to affected area 5 times/day X 5 days~~	Lipsovir Apply to affected area five times daily for five days
Outpatient Written Prescription: Lipsovir #1 Apply to affected area 5 times a day for 5 days	

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 applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provide an overall risk of name confusion.

Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6]

When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system.

FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective then remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A.

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

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 mode.

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

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

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

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

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

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Sponsor, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Sponsor's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, we believe that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

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

2.2 Label and Labeling Risk Assessment

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

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[1]

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

For this product the Applicant submitted on September 30, 2008 the following labels and labeling for DMEPA to review (see Appendices L and M)

- Container Label: 2 g and 5 g
- Carton Labeling: 2 g and 5 g
- Package Insert (no image)

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

For this review, DMEPA identified 31 names as having some similarity to the name Lipsovir. The names Cipro XR, Retrovir, Hipover, Tipranavir, Zipsor, Dapsone, Lipotriad, Lipocin, b(4)
[redacted], Lopurin, Liposyn II, Lipsorex, Saquinavir, Lipoicare, Lyovac, Lopressor, Trizivir, Hepsera, Heparin, and Diprivan were thought to look like Lipsovir. The names Indinavir, Darunavir, Tenofovir, LiquiTears, and Cidofovir were thought to sound similar to Lipsovir and the names Lipitor, Lipisorb, Lopinavir, Lipsovir, Levemir and Lepravir were thought to look and sound like Lipsovir.

A search of the United States Adopted Name (USAN) stem list on December 3, 2008 identified the USAN stem name, '-vir' within the proposed name, Lipsovir.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by DMEPA (see section 3.1 above), and noted no additional names. The panel discussed the presence of the USAN stem '-vir'. The panel also raised concerns regarding the oral ingestion of the cream which could occur if heavily applied to the mouth and lip area, proper labeling was suggested to remedy this concern.

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 27 practitioners responded, and none of the responses overlapped with any existing or proposed drug names. About 70 percent of the participants (n=19) interpreted the name correctly as "Lipsovir," with correct interpretation occurring more frequently in the written outpatient studies. The remainder of the responses misinterpreted the drug name. The majority of

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

misinterpretations occurred in the voice study, with the first syllable 'Lip' being misinterpreted as 'Whip', the syllable 'so' misinterpreted as 'se' or 'sa' and the last syllable 'vir' was misinterpreted as 'vere', sin or som. 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 similar to and represent a potential source of drug name confusion to Lipsovir. Additionally, we note that attempts to identify the drug names Lipocin and [redacted] were unsuccessful. We assume that these names were misspelled during the search process (i.e. Lipocin for Lipoicin and [redacted] for Lipoicare). Thus, we evaluated Lipoicin and Lipoicare (identified by the primary safety evaluator). As such, a total of 31 names were reviewed for look alike and sound alike similarity and if the drug name confusion would likely result in a medication error (Appendices D through J). b(4)

Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name, Lipsovir, could potentially be confused with any of the 31 names and lead to medication error.

FMEA determined that the name similarity between Lipsovir and the identified names was unlikely to result in medication errors for all 31 products (see Appendices D through K for our evaluation). However a search of the USAN website revealed that this name contains a USAN stem. See Section 4.1 for a full discussion regarding USAN stems and proprietary names.

3.2 LABEL AND LABELING RISK ASSESSMENT

3.2.1 Container Label

The net quantity is located next to the name.

There is no recommended route of administration.

Both w/w and mg are used to describe the strength of each product.

The established name is presented incorrectly.

3.2.2 Carton Labeling

The net quantity is located next to the name.

There is no recommended route of administration.

There is no warning to use only on mouth area.

Both w/w and mg are used to describe the strength of each product.

The established name is presented incorrectly.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

Our evaluation noted that the proposed name, Lipsovir, contains the United States Adopted Name (USAN) stem '-vir'. Use of USAN stems in proprietary names, even when used consistently with the USAN meaning, can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the chance of confusion among those drugs. To reduce the potential for confusion, USAN stems should not be incorporated into proprietary names.

The USAN Council (tri-sponsored by the American Medical Association (AMA), the United States Pharmacopeial Convention (USP), and the American Pharmacists Association (APhA)) works closely with the International Nonproprietary Name (INN) Programme of the World Health Organization (WHO) and various national nomenclature groups to achieve global standardization and unification of drug nomenclature and related rules with the goal of ensuring that drug information is communicated accurately and unambiguously.

The goal of the USAN program is to provide meaningful, informative designations for compounds, enhancing correct prescribing practices and patient safety. The listing of USAN stems represents common stems for which chemical and/or pharmacologic parameters have been established. These stems and their definitions, approved by the USAN Council, are recommended for use in coining new nonproprietary names for drugs that belong to an established series of related agents. By adopting this system, similar compounds maintain a common "family" name that provides immediate recognition.

Because the USAN stems are intended to indicate a pharmacological or chemical trait of a drug, a single stem will be applicable to multiple drug products. Use of these stems in proprietary names, even when used consistently with the USAN meaning, can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the chance of confusion among those drugs. To reduce the potential for confusion, USAN stems should not be incorporated into proprietary names. FDA recommends that applicants screen potential proprietary names against the USAN stem list and eliminate those that would incorporate USAN stems.

We note that there are numerous proprietary names currently approved (See Appendix B) which end with the stem '-vir'. Many of these names are also found on the USP list of similar names which have resulted in medication errors. DMEPA believes that continued approval of proprietary names incorporating the USAN stem "vir" will further contribute to this problem and undermine the USAN stems policy's ability to convey meaningful, informative designations for compounds.

Additionally, the USAN definition of the stem '-vir' is antiviral. This defines the acyclovir component of the name. However this stem is inappropriate for the other active ingredient, Hydrocortisone.

4.2 LABELS AND LABELING RISK ASSESSMENT

Our analysis of the labels and labeling noted several areas of needed improvement.

4.2.1 Container Label and Carton Labeling

The correct presentation of the established name should consist of the following format (in concurrence with the CMC review), as Lipsovir is a combination product; Acyclovir and Hydrocortisone Cream, 5%/1%. The font size of the strength, 5%/1% should be increased.

The strength is presented in both w/w and mg. Although this product is dosed in terms of small amount applied to the affected area, one measurement of strength (either w/w or mg) should be chosen and utilized consistently through the label and labeling to avoid confusion.

We noted the net quantity of 2 g or 5 g is located next to the proposed proprietary name, Lipsovir. This is problematic because this is typically where the strength is located. Placing the net quantity in this position could lead to misinterpretation of the number as the strength. To minimize this risk the net quantity should be relocated away from the proprietary name, established name and strength.

To ensure that the label and labeling are in accordance with 21 CFR 201.100 (b)(3) the statement, 'for external use only' should be prominently displayed on the primary display panel so that patients and practitioners are aware of the route of administration.

4.2.2 Application of Lipsovir and Dosing

The usual dosage section does not include the route of administration (i.e., topical) in the instructions. Because this medication could be confused for other types of herpes medications it is imperative to clarify that it is for topical usage.

This product will be used for herpes sores around the mouth and lip area only, however the label does not highlight this area of application. This medication will most likely be written with a signature of 'apply to affected area' instead of specifically the mouth area, therefore it would be important to add a warning highlighting the specific area of application.

5 CONCLUSIONS

The Division of Medication Error Prevention and Analysis (DMEPA) does not recommend the use of the proposed proprietary name, Lipsovir, because it contains the USAN stem '-vir'. The USAN definition of the stem '-vir' is antiviral, although this does define one of the ingredients in Lipsovir, it does not reflect the other active ingredient, Hydrocortisone.

Additionally, we have noted several areas of needed improvement with the labels and labeling. We provided recommendations in Section 5.2 below.

5.1 COMMENTS TO THE DIVISION

Please copy us on any communication to the Applicant with regard to this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Marlene Hammer, Project Manager, at 301-796-0757.

5.2 COMMENTS TO THE APPLICANT

A. Proprietary Name

We have completed our review of the proposed name, Lipsovir, and have concluded that it is unacceptable because it contains the United States Adopted Name (USAN) stem '-vir'. This stem is used by USAN to indicate an antiviral drug. Although Lipsovir is a proposed antiviral product and its use is consistent with the intended USAN meaning, the USAN council uses this stem for established names only.

The use of stems in proprietary names can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the chance of confusion among those drugs which may compromise patient safety. Additionally, the USAN stem, vir, identifies only one of the ingredients in Lipsovir, and does not indicate the product, Hydrocortisone.

To reduce the potential for confusion, USAN stems should not be incorporated into proprietary names. We recommend you screen potential proprietary names against the USAN stem list and eliminate those that incorporate USAN stems

B. Labels and Labeling

1. The net quantity of 2 g or 5 g is presented next to the proposed proprietary name, Lipsovir. This should be relocated away from the name to ensure that practitioners do not confuse the net quantity with the strength of the product.
2. Include the route of administration (i.e., topical) prominently on the primary display panel of the container label and carton labeling and in the usual dosage instructions as this medication could be confused for other types of herpes medications and ingested or inserted.
3. One measurement of strength (either w/w or mg) should be chosen and utilized throughout the label, labeling and package insert to ensure consistency and avoid confusion among practitioners and patients.
4. Presentation of the established name should be as follows; (Acyclovir and Hydrocortisone Cream) 5%/1%. Additionally, the strength should be increased in size.
5. The label should highlight the specific area of application, as herpes sores manifest in different areas and practitioners are likely to write the signature as apply to affected area, instead of specifically stating the mouth area.

6 REFERENCES

1. **MICROMEDEX INTEGRATED INDEX** (HTTP://WEBLERN/)

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

3. **Drug Facts and Comparisons, online version, St. Louis, MO** (http://weblern/)

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

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

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

5. **Division of Medication Error Prevention proprietary name consultation requests**

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.

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. **US Patent and Trademarks Office** http://www.uspto.gov.

Provides information regarding patent and trademarks.

9. **Clinical Pharmacology Online** (http://weblern/)

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

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

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

11. Natural Medicines Comprehensive Databases (http://weblern/)

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

12. Stat!Ref (http://weblern/)

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

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

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

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

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The medication error staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. We also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The medication error staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The medication error staff 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, the medication error staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, we will consider the Sponsor's intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, we also consider a variety of pronunciations that could occur in the English language.

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

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• 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 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: Proprietary names ending with the letters "-vir"

Proprietary Name	Established Name	Date of First Approval	Reviewed by DMEPA? (Yes or No)	Post-marketing confusion with other names ending in -vir
Combivir	lamivudine/zidovudine	9/26/1997	No	Yes (Epivir)
Denavir	penciclovir	9/24/1996	No	Yes (Indinavir)
Epivir	lamivudine	11/17/1995	No	Yes (Combivir)
Famvir	famciclovir	6/29/1994	No	-
Foscavir	foscarnet	9/27/1991	No	-
Norvir	ritonavir	3/1/1996	No	Yes (Retrovir)
Retrovir	zidovudine	3/19/1987	No	Yes (Norvir; Ritonavir)
Trizivir	abacavir/lamivudine/zidovudine	11/14/2000	Yes	-

Appendix C: CDER Prescription Study Responses, Study 1204

Inpatient-Sample 1	Outpatient-Sample 2	Voice
Liposin	Lipsovir	Lipsovere
Lipsovir	Lipsovir	Lipsovir
Lipsovir	Lipsovir	Lipsovir
Lipsovir	Lipsovir	Whipsevere
Lipsovir	Lipsovir	Lipsevere
Lipsovir	Lipsovir	Wipsovere
Lipsovir	Lipsovir	Lipsovir
Lipsom	Lipsovir	Lipsavir
Lipsovir		Lipsovir
		Lipsevere

Appendix D: Name is only one component of combination drug product and would not be referred to as the single agent.

Proprietary Name	Similarity to Lipsovir	Reason
Lopinavir	Both look and sound	Lopinavir is not available as a single agent, only marketed with Ritonavir and marketed as Kaletra

Appendix E: United States Patent and Trademark office name listed as "Live" form the same Applicant that submitted the name Lipsovir.

Proprietary Name	Similarity to Lipsovir
Lipsovir	Both

Appendix F: Drug marketed only in foreign markets

Proprietary Name	Active Ingredients	Foreign Market
Lipsorex and Lipsorex Plus	Benzethonium chloride, Lidocaine, Menthol, Thymol	Canada
Hipover	Repaglinide	Chile

Appendix G: Drug application withdrawn and no generic available

Proprietary Name	NDA #	Year withdrawn
Lyovac	3-256	1971

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

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Lipsovir (Acyclovir, Hydrocortisone)		**5%/1% Cream;**	**Apply to affected area 5 times daily for 5 days**
Cipro XR (Ciprofloxacin hydrochloride)	Look	500 mg, 1000 mg Extended-release oral tablets	Uncomplicated Urinary Tract Infection: 500 mg orally once daily for 3 days Complicated Urinary Tract Infection: 1000 mg orally once daily for 7 to 14 days Acute Uncomplicated Pyelonephritis: 1000 mg orally once daily for 7 to 14 days
Retrovir (Zidovudine)	Look	300 mg oral tablets, 100 mg capsules, 50 mg/5 mL oral syrup; 240 mL 10 mg/mL; 20 mL single use vial	Adults: 600 mg orally in divided doses, with other antiretroviral agents Pediatrics 6 weeks to 12 years: 1600 mg/meter squared orally every 8 hours, with other antiretrovirals Renal impairment: 100 mg orally every 6 to 8 hours Intravenous infusion: 1 mg/kg over 1 hour 5 to 6 times daily Maternal dosing: 2mg/kg intravenously over 1 hour followed by continuous infusion, until clamping umbilical cord Neonatal dosing: 1.5mg/kg intravenously over 30 minutes every 6 hours
Lopurin (Allopurinol)	Look	100 mg, 300 mg oral tablet	200 mg to 800 mg orally per day in divided doses (if greater then 300 mg per day)
Heparin	Look	100 units/mL, 10 units/ 10 mL, 10 units/30 mL, 100 units/10 mL, 100 units/ 30 mL, 1,000 units/mL, 5,000 units/mL, 10,000 units/mL, 7,500 units/0.75 mL, 5,000 units/0.5 mL 25,000 units/250 mL 12,500 units/250 mL 25,000 units/500 mL 20,000 units/500 mL 25,000 units/500 mL	Subcutaneous: 5000 to 20000 units every 8 hours to 12 hours based on response Intermittent intravenous injection: 5000 to 10000 units every 4 to 6 hours Continuous intravenous infusion: 5000 units initial dose, then 20,000 to 40,000 units every 24 hours, titrated for response

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Lipsovir (Acyclovir, Hydrocortisone)		**5%/1% Cream;**	**Apply to affected area 5 times daily for 5 days**
Indinavir (Brand name, Crixivan)	Sound	100 mg, 200 mg, 333 mg, 400 mg oral capsules	800 mg orally every 8 hours While taking Delavirdine, Didanosine, Itraconazole, Ketoconazole, Rifabutin: 600 mg orally every 8 hours Hepatic insufficiency: 600 mg orally every 8 hours
Darunavir (Brand name, Prezista)	Sound	300 mg, 400 mg, 600 mg oral tablet	Adults: (naïve) 800 mg orally with 100 mg Ritonavir once daily, (experienced) 600 mg orally with 100 mg Ritonavir twice daily
Lipitor (Atorvastatin calcium)	Both	10 mg, 20 mg, 40 mg, 80 mg oral tablet	Pediatric patients (10 to 17 years of age): 10 mg to 20 mg orally once daily Adults: 10 mg to 80 mg orally once daily
Lepravir (Dapsone) (ANDA approval 1979)	Both	25 mg, 100 mg oral tablet	Dermatitis herpetiformis: 50 mg to 300 mg orally daily Leprosy: 100 mg orally daily (with other anti-leprosy medications) Pneumocystis pneumonia: 50 mg orally twice daily or 100 mg once daily with additional medications Toxoplasmosis: 50 mg orally once daily or 200 mg orally once weekly
Liposyn II 10%, 20% (Safflower oil and Soybean oil)	Look	5%; 5 gm/100 mL 10%; 10 gm/100 mL intravenous solution	Lipid infusion for parenteral nutrition
Lopressor (Metoprolol tartrate)	Look	50 mg, 100 mg oral tablet 5 mg/5 mL ampule	Hypertension: 100 mg to 450 mg orally per day in single or divided doses Angina Pectoris: 100 mg to 400 mg orally per day in two divided doses Myocardial Infarction: (early treatment) three bolus intravenous injections of 5 mg or 50 mg orally every 6 hours. (late treatment) 100 mg orally twice daily

Appendix I: Products with a single strength or an overlapping strength but multiple differentiating product characteristics

Product name with potential for confusion	Similarity to Product Name	Strength	Usual Dose (if applicable)	Other differentiating product characteristics
Lipsovir (Acyclovir, Hydrocortisone)		**5%/1% Cream;**	**Apply to affected area 5 times daily for 5 days**	
Tipranavir (Brand name, Aptivus)	Look	250 mg oral capsule	500 mg orally (co-administered with Ritonavir) twice daily	Route of administration (topical vs. oral) Frequency of administration (5 times daily vs. twice daily) Dosage form (cream vs. capsule) Context of therapy (Tipranavir must be taken with Ritonavir for proper HIV suppression and must be taken with other HIV medications)
Saquinavir (Brand name Fortovase)	Look	200 mg oral capsule	With Ritonavir: 1000 mg orally twice daily Without Ritonavir: 1200 mg orally three times daily	Route of administration (topical vs. oral) Frequency of administration (5 times vs. once or twice daily) Dosage form (cream vs. capsule) Context of therapy (Saquinavir must be taken with other HIV medications to achieve HIV suppression)
Hepsera (Adefovir dipivoxil)	Look	10 mg oral tablet	10 mg orally once daily, for renal decrease frequency by 24 hours (up to once weekly for hemodialysis)	Route of administration (topical vs. oral) Frequency of administration (5 times daily vs. once daily) Dosage form (cream vs. tablet)
Lipisorb	Both	Enteral nutrition therapy, powder	As directed for nutritional supplement	Route of administration (oral vs. topical) Dosage form (cream vs. powder for oral solution)

Product name with potential for confusion	Similarity to Product Name	Strength	Usual Dose (if applicable)	Other differentiating product characteristics
Lipsovir (Acyclovir, Hydrocortisone)		**5%/1% Cream;**	**Apply to affected area 5 times daily for 5 days**	
Cidofovir (Brand name, Vistide)	Sound	75 mg/mL; 5 mL single use vial	Induction treatment: 5 mg/kg administered once weekly for 2 weeks Maintenance treatment: 5 mg/kg once every 2 weeks Decreased renal function: 3 mg/kg to 5 mg/kg once weekly	Route of administration (topical vs. intravenous) Frequency of administration (5 times daily vs. once weekly) Dosage form (cream vs. single use vial)
Tenofovir (Viread)	Sound	300 mg oral film coated tablet	300 mg orally once daily, increase frequency for creatinine clearance to every 48 hours to once weekly	Route of administration (topical vs. oral) Frequency of administration (5 times daily vs. once daily) Dosage form (cream vs. tablet)
Diprivan (Propofol)	Look	10 mg/mL; 20 mL, 50 mL, 100 mL single use vials	Dose and rate of administration are individualized and titrated to desired effect, start at 0.3 mg/kg/hour	Route of administration (topical vs. intravenous) Frequency of administration (5 times daily vs. titrated for response) Dosage form (cream vs. single use infusion vial)
Zipsor *** (Diclofenac)	Look	25 mg oral capsule	25 mg orally every 6 hours as needed for pain	Route of administration (topical vs. oral) Frequency of administration (5 times daily vs. as needed, up to 4 times daily) Dosage form (cream vs. capsule)
Lipotriad	Look	Multivitamin plus 250 mcg Lutein oral caplet	One caplet once daily	Route of administration (topical vs. oral) Frequency of administration (5 times daily vs. once daily) Dosage form (cream vs. caplet)
Liquitears (Polyvinyl alcohol)	Sound	1.4% Ophthalmic solution	1 drop to 2 drops in each eye as needed	Route of administration (topical vs. eyes) Frequency of administration (5 times daily vs. as needed for symptoms) Dosage form (cream vs. solution)

Product name with potential for confusion	Similarity to Product Name	Strength	Usual Dose (if applicable)	Other differentiating product characteristics
Lipsovir (Acyclovir, Hydrocortisone)		**5%/1% Cream;**	**Apply to affected area 5 times daily for 5 days**	
[redacted]	Look	[redacted]	[redacted]	Route of administration (topical vs. [redacted] Dosage form (cream vs. [redacted] Duration of use (5 days vs. [redacted]
Levemir (insulin Detemir)	Both	100 units/mL; 10 ml vial, 3 mL PenFill, 3 mL InnoLet, 3 mL FlexPen	Subcutaneously once or twice daily based on glucose measure	Route of administration (topical vs. subcutaneous) Dosage form (cream vs. solution) Frequency of administration (5 times daily vs. once or twice daily)
Lipoicin (Alpha-Lipoic acid)	Look	50 mg, 100 mg, 300 mg, 600 mg capsule 5 % topical cream Intravenous solution	Diabetes and peripheral neuropathy: 600 mg to 1200 mg daily Cardiac autonomic neuropathy: 800 mg orally daily Peripheral arterial disease: 300 mg orally twice daily Apply twice daily to wrinkles 600 mg to 1200 mg intravenously for peripheral neuropathy	Frequency of administration (5 times daily vs. twice daily) Prescription status (Rx vs. Over the Counter) Duration of use (5 days vs. no limit)

b(4)

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

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

Lipsovir (Acyclovir-Hydrocortisone)	5%-1% Cream, 2 gram-5 gram tube	Usual dose: Apply to affected area 5 times daily for 5 days
Failure Mode: Name Confusion	**Causes (could be multiple)**	**Effects**
Dapsone (Brand name, Aczone) 5% gel; 3 gram, 30 gram Apply topically to affected area twice daily	Orthographic similarity: names share same downstroke as third letter ('Dap' vs. 'Lip'), both names have the similar number of letters (seven vs. eight). Overlapping strength (5%). Same dosage form (cream) and route of administration (topical).	Differing product and orthographic characteristics minimize the likelihood of medication error in the usual practice setting. *Rationale*: The recommended frequency for Lipsovir is 5 times daily vs. twice daily for Dapsone. Lipsovir is also limited to 5 days of use, Dapsone is used indefinitely. Orthographically, Lipsovir contains two dotted 'i's vs. none in Dapsone. Dapsone begins with 'Da' vs. 'Li' of Lipsovir. The 'Da' component consumes more space when written in comparison to 'Li' which are narrow letters. Although the letters 'one' when scripted could resemble 'ovi' the 'r' ending lengthens the segment and helps differentiate Lipsovir and Dapsone.

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