CENTER FOR DRUG EVALUATION AND RESEARCH

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PROPRIETARY NAME REVIEW(S)

Department of Health and Human Services
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From:	Cathy A. Miller, MPH, BSN, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name(s):	Gadavist (Gadobutrol) Injection 1 mmol Gadobutrol/mL (equivalent to 604.72 mg/mL)
Applicant	Bayer Healthcare Pharmaceuticals, Inc.
OSE RCM #:	2011-406

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EXECUTIVE SUMMARY

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA's) proprietary name risk assessment of Gadavist for Gadobutrol Injection. Our evaluation did not identify concerns that would render the name unacceptable based on product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name, Gadavist, acceptable for this product.

The proposed proprietary name must be re-reviewed if the NDA is not approved within 90 days of the signature date of this review. If any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a request from Bayer Pharmaceuticals, Inc., dated February 18, 2011, for an assessment of the proposed proprietary name, Gadavist, regarding the promotional nature and potential name confusion with other proprietary or established drug names in the usual practice setting.

1.2 REGULATORY HISTORY

Gadobutrol was approved in Switzerland in February 1998 under the proprietary name, Gadovist, and has marketed in most of Europe as Gadovist, including 65 countries since 2000. In many countries, '1.0' or '1.0 M' follows the proprietary name, Gadovist, to further emphasize the higher concentration of Gadobutrol compared to other Gadolinium-based Contrast Agents (GBCAs).

The Applicant submitted a request for review of the proposed names, Gadovist 1.0 and Gadovist, during the IND phase of the development of this product (IND 056410) were found unacceptable by DMEPA in OSE-RCM Review #2010-457, dated August 13, 2010, (b) (4)

On December 2, 1010, the Applicant submitted a request for review of the proposed proprietary name, (b) (4) along with labels and labeling. DMEPA found no safety concerns associated with look-alike or sound-alike names identified during our analysis nor did Division of Drug Marketing Advertising and Communication (DDMAC) did not identify any promotional concerns with the name. However, the Division of Medical Imaging Products (DMIP) raised concerns that the (b) (4)

On February 8, 2011, a teleconference was conducted between DMEPA, DMIP and the Applicant. DMIP and DMEPA communicated the concerns raised by DMIP and the Applicant agreed to withdraw the proposed proprietary name, (b) (4) and submit an alternate name.

On February 10, 2011, the Applicant submitted a request to withdraw their request for review of the proposed proprietary name, (b) (4)

On February 18, 2011, the Applicant submitted a request for review of the proposed name, Gadavist.

1.3 PRODUCT INFORMATION

Gadavist is a Gadolinium-based contrast agent indicated for intravenous use in diagnostic magnetic resonance imaging (MRI) in adults and children (2 years of age or older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system.

Gadavist is a macrocyclic GBCA, formulated at a higher concentration (1 mmol/mL) compared to other extracellular Gadolinium-based contrast agents (0.5 mmol/mL). This results in half the volume needed for administration per kg body weight (0.1 mL/kg) for central nervous system (CNS) indications. In their submission, the Applicant states that the higher concentration was used due to the physico-chemical properties of Gadobutrol, including solubility, hydrophilicity and osmolarity and is the only GBCA which can be formulated in a 1 Molar concentration while maintaining acceptable viscosity similar to other available extracellular GBCAs. Table 1 below outlines the varying strengths for the currently marketed GBCA products with CNS indications.

Table 1. Five Marketed GBCAs With CNS Indications

Trade Name	Molar	Dosing Regimen (mmol/kg)	
		Adults	Pediatrics
Magnevist	0.5	0.1	0.1 (> 2 y.o.)
Prohance	0.5	0.1 CNS (optional 2nd dose 0.2)	0.1 (> 2 y.o.)
Omniscan	0.5	0.1	0.1 (> 2 y.o.)
Optimark	0.5	0.1	N/A
Multihance	0.5	0.1	0.1 (> 2 y.o.)
Gadovist	**1.0**	**0.1**	**0.1 (> 2 y.o.)**

Gadavist is a sterile, clear, colorless to pale yellow solution for injection containing 1 mmol Gadobutrol per milliliter (equivalent to 604.72 Gadobutrol/mL). Gadavist is supplied in single-dose (RFID) vials and single-dose disposable syringes of 7.5 mL, 10 mL and 15 mL, along with pharmacy bulk packages of 30 mL and 65 mL (RFID) bottles. Gadavist should be stored at 25° C (77° F). If freezing occurs, Gadavist should be brought to room temperature before use.

Table 2 on the next page illustrates the volume of Gadavist to be administered based on body weight. Gadavist should be administered as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 2 mL per second.

Table 2: Gadavist dosing (mL/kg) body weight

VOLUME OF TRADENAME INJECTION BY BODY WEIGHT		
BODY WEIGHT		Total Volume, mL*
lb	kg	
22	10	1
33	15	1.5
44	20	2
55	25	2.5
66	30	3
77	35	3.5
88	40	4
99	45	4.5
110	50	5
132	60	6
154	70	7
176	80	8
198	90	9
220	100	10
242	110	11
264	120	12
286	130	13
298	140	14

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1, 2.2, and 2.3 identify specific information associated with the methodology for reviewing the proposed proprietary name, Gadavist

2.1 SEARCH CRITERIA

For this review, a particular consideration was given to drug names beginning with the letter 'G' 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.[1,2]

To identify drug names that may look similar to Gadavist, the DMEPA safety evaluators also consider the orthographic appearance of the name on the lined and unlined orders. Specific

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

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

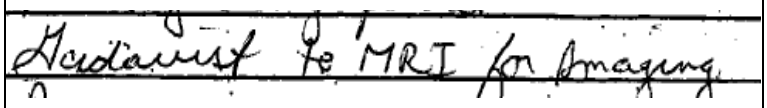
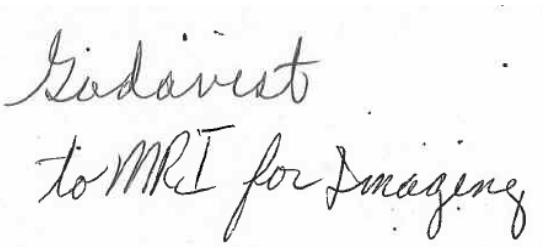
attributes taken into consideration include the length of the name (eight letters), upstrokes (three, the first letter G, lower case letter 'd' and lower case letter 't'), down strokes (one, the lower case letter 'g'), cross-strokes (one, lowercase letter 't'), and the dotted letters (one, lower case letter 'i'). Additionally, several letters in the proposed name, Gadavist, may be vulnerable to ambiguity when scripted (See Appendix B). As such, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Gadavist.

When searching to identify potential names that may sound similar to Gadavist, the DMEPA safety evaluators search for names with similar number of syllables (three), stresses (GAD-a-vist, gad-A-vist and gad-a-VIST), and placement of vowel and consonant sounds. The Applicant provided the intended pronunciation of the name as 'Gad-ah-vist'. Additionally, DMEPA safety evaluators consider that pronunciation of part of the name can vary (Appendix B). Additionally, names are often mispronounced or spoken with regional accents and dialects, so other pronunciations of the names are considered.

2.2 FDA PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient and verbal orders were communicated during FDA prescription studies on February 10, 2011.

Figure 1: Gadavist Study Sample

Handwritten Requisition Medication Order	Verbal Prescription
Inpatient Medication Order:  Gadavist to MRI for Imaging	Gadavist to MRI for Imaging
Outpatient Medication Order:  Gadavist to MRI for Imaging	

3 RESULTS

The following sections describe the results of the proprietary name analysis that were identified during this review.

3.1 DATA BASE AND INFORMATION SOURCES

The DMEPA safety evaluators searches yielded a total of twenty (n=20) names as having some similarity to the name, Gadavist.

Seven (n=7) of the twenty names were thought to look like Gadavist by the safety evaluators. These names are Caduet, Gardasil, Gastrinex, Gastrosed, Genliet, Gentasol, and Genteal.

Seven (n=7) of the twenty names were thought to sound like Gadavist by the safety evaluators. These names are Galvus, Magnevist, Omnaris, Renovist, Tavist, Ultravist and Urovist.

Six (n=6) of the twenty names were thought to look and sound like Gadavist by the safety evaluators. These names are Angiovist, Calomist, Gadovist, Gastrovist, Osmovist and Vasovist.

Additionally, DMEPA did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name as of February 11, 2011.

3.2 EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA staff (see Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Gadavist.

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

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

A total of 41 practitioners responded to the prescription analysis studies. We note that five respondents interpreted the drug name as 'Gadovist' which is the proprietary name previously submitted by the Applicant and is also the proprietary name used for the same product marketed in Europe. No other interpretations overlapped with currently marketed drug products. Twelve (n=12) respondents interpreted the proposed name correctly as 'Gadavist' with correct interpretation occurring equally in the written and verbal studies. Other common interpretations included the letter 'a' as the letter 'o' and the omission of the last letter 't'. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

3.5 COMMENTS FROM THE DIVISION OF MEDICAL IMAGING PRODUCTS

3.5.1 INITIAL PHASE OF REVIEW

During the February 8, 2011 teleconference with the Sponsor to discuss concerns with the proposed proprietary name, (b) (4) the Applicant and DMEPA discussed options for alternate proprietary names. One name discussed during the teleconference was the proposed name, Gadavist. At that time, DMIP stated that they did not have concerns or objections with this proposed proprietary name.

3.5.2 MIDPOINT OF REVIEW

DMEPA notified DMIP via email that we do not object to the use of the proprietary name, (b) (4) on Wednesday, February 23, 2011. On Friday, February 25, 2011, DMIP responded via email that they had no concerns or objection to the proposed proprietary name, Gadavist.

3.6 SAFETY EVALUATOR RISK ASSESSMENT OF THE PROPOSED PROPRIETARY NAME

The primary safety evaluator identified an additional two names (n=2), which were thought to look similar to Gadavist and represent a potential source of drug confusion. These names are Cida-stat and Somavert.

In total, twenty-two (n=22) names were identified as potentially similar to the proposed name, Gadavist (i.e. twenty (n=20) names from database searches and two (n=2) from the safety evaluator).

4 DISCUSSION

The proposed proprietary name, Gadavist, was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input

from pertinent disciplines involved with the review of this application and considered it accordingly.

4.1 PROMOTIONAL ASSESSMENT

DDMAC did not find the name Gadavist promotional and communicated these findings to DMEPA on Thursday, February 24, 2011. DMEPA and DMIP concurred with these finding.

4.2 SAFETY ASSESSMENT

In total, DMEPA evaluated twenty-two (n=22) names. Twelve (n=12) of the 22 names were eliminated from the further analysis for the following reasons: One name was found to be the same product marketed in multiple European countries, nine names lacked convincing orthographic and/or phonetic similarity to the proposed name, Gadavist, one name was found to be a discontinued product with no generics available and one name was found to be a proposed name reviewed by DMEPA and found acceptable, but an alternate proprietary names was selected for the product. (See Appendix D for details).

Failure Mode and Effect Analysis (FMEA) was then applied to determine of the proposed proprietary name could potentially be confused with the remaining ten (n=10) names, thereby, lead to medication errors. This analysis determined that the name similarity between Gadavist was unlikely to result in medication errors with any of the ten remaining products for the reasons presented in Appendix E.

5 CONCLUSIONS AND RECOMMENDATIONS

Our assessment of the proprietary name indicates that the proposed name, Gadavist, is not vulnerable to name confusion that could lead to medication errors, nor is the name considered promotional. Thus, DMEPA has no objection to the proposed name, Gadavist, for this product at this time. The Applicant will be notified via letter.

Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

If you have further questions or need clarifications, please contact Sandra Griffith, Project Manager, at 301-796-2445.

5.1 COMMENTS TO THE APPLICANT

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

The proposed proprietary name must be re-reviewed 90 days before approval of the NDA. If any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

6 REFERENCES

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

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

2. Phonetic and Orthographic Computer Analysis (POCA)

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

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

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

4. The Document Archiving, Reporting, and Regulatory Tracking System (DARRTS)

DARRTS 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, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. 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.

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

USPTO provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also 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)

Natural Medicines 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)

Stat!Ref contains full-text information from approximately 30 texts; it 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)

USAN Stems List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. 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. [3]

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

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. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [4] DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used 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. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

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

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

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

monitoring the impact of the medication.[5] DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis 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 in spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 3 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice.

Table 3. **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 Down strokes	• Names may look similar when scripted, and lead to drug name confusion in written communication

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

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

Lastly, the DMEPA staff also considers the potential for the proposed proprietary 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. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA staff conducts searches 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 Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff 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 primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Analysis Studies

Two separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name 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 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 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.

4. Comments from the OND review Division or Generic drugs

DMEPA requests the Office of New Drugs (OND) or Office of Generic Drugs (OGD) Regulatory Division 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. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

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

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment 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 proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug

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

name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar 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 primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. 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 Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name 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 the proposed proprietary name 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, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes 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 not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name 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 the use of an alternate proprietary name.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

a. 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 PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

b. 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)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), <u>and</u> demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, 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.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor 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 Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

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, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative 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 a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, 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 Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, 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 Section 4 for 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 primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor 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 Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

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, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in the name Gadavist	Scripted may appear as	Spoken may be interpreted as
Capital 'G'	Capital C, O, S	
Lower case 'a'	Any lowercase letter that does not have a upstroke or downstroke	Any vowel sound
Lower case 'd'	b, h, l or t	t
Lower case 'v'	Any lowercase letter that does not have a upstroke or downstroke	b
Lower case 'i'	e or l	Any vowel sound
Lower case 's'	Any lowercase letter that does not have a upstroke or downstroke	c or z
Lower case 't'	b,h, d, i, l, or t	d

Appendix C: Gadavist Prescription Study Results conducted on February 10, 2011

Inpatient Study	Outpatient Study	Verbal Study
Gadavist	Gadavest	Gadevah
Gadavist	Gadavest	Gadovist
Gadavist	Gadavist	Gadovist
Gadavist	Gadavist	Gatavis
Gadavist	Gadavist	Gatavis
Gadovist	Gadavist	Gatavis
Gaidavist	Gadavist	Gatavis
Gardavist	Gadavist	Gatavist
Gardavist	Gadavist	Gatavist
Gardavist	Gadovist	Gatavist
Geidavist	Gadovist	Gatavist
Gerdavist	Giadavist	Gatavist
	Gidavest	Gatavist
	Godavist	Gatavith
		Gativist

Appendix D: Names eliminated from further evaluation for reasons listed below

	Proprietary Name	Similarity to Gadavist	Active Ingredient	Reason Eliminated
1	Angiovist	Look- and Sound-alike	Diatrizoate Meglumine and Diatrizoate Sodium	Lacks convincing orthographic or phonetic similarity to the proposed name Gadavist
2	Caduet	Look-Alike	Amlodipine Besylate and Atrovastatin Calcium	Lacks convincing orthographic similarity to the proposed name Gadavist
3	Gadovist	Both	Gadobutrol	Same product manufactured by Bayer available in Europe; not marketed in the U.S.
4	Galvus***	Look-Alike	Vildagliptin	Lacks convincing orthographic similarity to the proposed name Gadavist
5	(b) (4)			
6	Magnevist	Sound-Alike	Gadopentetate Dimeglumine	Lacks convincing phonetic similarity to the proposed name Gadavist
7	Omnaris	Sound-Alike	Ciclesonide	Lacks convincing phonetic similarity to the proposed name Gadavist
8	Osmovist	Look-Alike	Iotrolan	Discontinued; no generics available
9	Tavist	Sound-Alike	Clemastine	Lacks convincing phonetic similarity to the proposed name Gadavist
10	Renovist	Sound-Alike	Diatrizoate Meglumine and Diatrizoate Sodium	Lacks convincing phonetic similarity to the proposed name Gadavist
11	Urovist	Sound-alike	Diatrizoate Melumine	Lacks convincing phonetic similarity to the proposed name Gadavist
12	Vasovist***	Look-Alike	Gadofosveset Trisodium	Proposed name #2008-1333 found acceptable by DMEPA;NDA 021711 approved 12/2008 under different proprietary name, Ablavar

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

Appendix E: Potentially confusing names with orthographic, phonetic or multiple differentiating product characteristics that decrease the risk of medication errors.

PROPOSED NAME: **Gadavist** (Gadobutrol)		**STRENGTH:** **1 mol/L or 1 mmol/mL in 10 mL vial (Equivalent to 604.72 mg/mL)**	**USUAL DOSE:** **0.1 mL/kg (0.1 mmol/kg)** **1 mL to 14 mL**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
13	**Calomist** (Cyanocobalmin) Nasal Spray Strength: 25 mcg/0.1 mL nasal spray Dose: One spray into each nostril once or twice daily	Orthographic similarity: The first letter 'C' can appear like the first letter 'G', the third upstroke letter 'l' can appear like the third upstroke letter 'd' and both names end with the letters 'ist'. Single strength	Varying product characteristics minimize the potential for confusion. No overlap in dose or strength Dosage form: Topical Nasal spray versus injection Route of administration: Topical versus intravenous
14	**Cida-stat** (Chlorhexidine Gluconate) Solution Strength: 2% and 4% Dose: Apply to skin, wash and rinse thoroughly	Orthographic similarities: Both names have eight letters. The first letter 'C' can appear like the first letter 'G'; both names contain the upstroke letter 'd' in the third letter position and the upstroke/cross-stroke letter 't' in the last letter position.	Orthographic differences in the names, along with variations in product characteristics minimize the potential for confusion Orthographic differences: There is an upstroke/cross-stroke letter 't' in the sixth letter position of Cida-stat that is not present in Gadavist that provides orthographic distinction. Differentiating product characteristics: Single strength versus multiple strength No overlap in dose Dosage form: Topical solution versus injection
15	**Gardasil** (Human Papillomavirus Quadrivalent Vaccine, Recombinant) Injection Strength: 0.5 mL suspension for injection Dose: 0.5 mL intramuscularly per injection given in a series of three injections at 0, 2 and 6 months	Orthographic similarities: Both names begin with the letter 'G', have an upstroke letter 'd' similarly placed and end similarly with an upstroke letter 'l' versus 't'. Overlapping product characteristics: Dosage form: Injection Single strength availability	Variations in product characteristics minimize the potential for confusion. There is no overlap in dose between the two products. Frequency of administration varies. Gardasil is given in a series of three injections (0 months, 2 months and again at 6 months) while Gadavist is administered once prior to imaging procedure.

Appendix E: Potentially confusing names with orthographic, phonetic or multiple differentiating product characteristics that decrease the risk of medication errors.

PROPOSED NAME: **Gadavist** (Gadobutrol)		**STRENGTH:** **1 mol/L or 1 mmol/mL in 10 mL vial (Equivalent to 604.72 mg/mL)**	**USUAL DOSE:** **0.1 mL/kg (0.1 mmol/kg)** **1 mL to 14 mL**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
16	**Gastrinex** Amylase (Porcine), Cellulase, Lipase (Porcine) , and Protease (Porcine) Capsules Strength: 30U/2 mg/ 1200U/6 mg Dose: Take on capsule with each meal or as directed by physician	Orthographic similarities: Both names begin with the letters 'Ga', and contain the upstroke letters 't' versus 'd' in similar letter positions of the name. Overlapping product characteristics: Single strength	Varying product characteristics minimize the potential for confusion. There is no overlap in dose between the two products Dosage form: Tablet versus injection Route of administration: Oral versus intravenous
17	**Gastrosed** (Hyoscyamine Sulfate) Tablets and Oral Solution Strength: 0.125 mg, 0.375 mg, 0.15 mg tablets 0.125 mg/5 mL oral solution Dose: One to two tablets every four hours; maximum dose of 1.5 mg daily 1 mL to 2 mL every four hours; maximum dose of 12 mL in twenty-four hours	Orthographic similarities: Both names begin with the letters 'Ga', contain an upstroke letter 't' versus 'd' similarly placed and end with an upstroke letter 'd' versus 't'. Overlapping product characteristics: Dose: '1 mL' and '2 mL'	Variation in product characteristics minimize the potential for confusion: Single strength versus multiple strengths Dosage form: Tablets and Oral Solution versus Injection Route of administration: Oral versus intravenous Frequency of administration: Every four hours versus one time administration prior to imaging procedure

Appendix E: Potentially confusing names with orthographic, phonetic or multiple differentiating product characteristics that decrease the risk of medication errors.

PROPOSED NAME: **Gadavist** (Gadobutrol)		**STRENGTH:** **1 mol/L or 1 mmol/mL in 10 mL vial (Equivalent to 604.72 mg/mL)**	**USUAL DOSE:** **0.1 mL/kg (0.1 mmol/kg)** **1 mL to 14 mL**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
18	**Gastrovist*** (Diatrizoate Meglumine and Diatrizoate Sodium) Oral solution and enema Strength: 66% /10% Dose: Oral: 30 mL to 90 mL Enema: Mix 240 mL in 1000 mL tap water and then instill *Generic Gastrovist discontinued but RLD Gastrografin still available	Orthographic and phonetic similarities: Both names begin with the letters 'Ga', there is an upstroke letter 't' versus 'd' in the fourth letter positions of the names and both names end with the letters 'ovist'. Both names contain three syllables and contain the 'Ga' sound in the first syllable, along with the 'vist' sound in the last syllable. Overlapping product characteristics: Imaging agents with similar use during radiographic examination Frequency of administration and use: One time use prior to imaging procedure Single strength availability	Orthographic and phonetic differences, along with variations in product characteristics minimize the Orthographic and phonetic differences: There are nine letters in the name Gadavist while there are ten letters in the name Gastrovist, making it appear longer when scripted. The hard 'o' sound in the second syllable of Gastrovist varies from the soft 'ah' sound in the second syllable of the name Gadavist. Differentiating product characteristics: No overlap in dose: 30 mL to 90 mL for oral administration versus 1 mL to 14 mL; or 1000 mL for enema administration versus 1 mL to 14 mL Dosage form: Oral solution or enema versus injection Route of administration: Oral or rectal enema versus intravenous The RLD product for this active ingredient, Gastrografin, is still marketed, however, Gastrovist, along with many other generics for this product are dicontinued. Because practitioners are likely to be most familiar with the RLD by the name 'Gastrografin, DMEPA believes the risk is minimal that practitioners will order or refer to this product by the name 'Gastrovist'.

Appendix E: Potentially confusing names with orthographic, phonetic or multiple differentiating product characteristics that decrease the risk of medication errors.

PROPOSED NAME: **Gadavist** (Gadobutrol)		**STRENGTH:** **1 mol/L or 1 mmol/mL in 10 mL vial (Equivalent to 604.72 mg/mL)**	**USUAL DOSE:** **0.1 mL/kg (0.1 mmol/kg)** **1 mL to 14 mL**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
19	**Gentasol** (Gentamicin) Ointment Strength: 0.3% Dose: Apply to affected eye every four hours or as directed by physician	Orthographic similarities: Both names begin with the letter 'G', the second letter 'e' can appear like the second letter 'a', both names contain an upstroke letter 't' versus 'd' similarly placed and end with an upstroke letter 'l' versus 't'. Overlapping product characteristics: Single strength availability	Variations in product characteristics minimize the potential for confusion. No overlap in dose Dosage form: Ophthalmic ointment versus injection Route of administration: Topical Ophthalmic versus intravenous Frequency of administration: Every four hours versus one time administration prior to imaging procedure
20	**Genteal** (Hypromellose) Ophthalmic Ointment, Gel and Drops Strength: 0.2% and 0.3% Dose: Apply to eyes daily or as directed by physician	Orthographic similarities: Both names begin with the letter 'G', the second letter 'e' can appear like the second letter 'a', both names contain an upstroke letter 't' versus 'd' similarly placed, and both names end with an upstroke letter 'l' versus 't'	Orthographic differences in the names, along with variations in product characteristics minimize the potential for confusion. There are seven letters in the name Genteal while there are eight letters in the name Gadavist making it appear longer when scripted. Differentiating product characteristics: Multiple strength versus single strength No overlap in dose Dosage form: Opthalmic ointment, gel and drops versus injection Route of administration: Ophthalmic topical versus intravenous Frequency of administration: Daily or Use as directed versus one time administration prior to imaging procedure

Appendix E: Potentially confusing names with orthographic, phonetic or multiple differentiating product characteristics that decrease the risk of medication errors.

PROPOSED NAME: **Gadavist** (Gadobutrol)		**STRENGTH:** **1 mol/L or 1 mmol/mL in 10 mL vial (Equivalent to 604.72 mg/mL)**	**USUAL DOSE:** **0.1 mL/kg (0.1 mmol/kg)** **1 mL to 14 mL**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
21	**Somavert** (Pegvisomant) For Injection Strength: 10 mg/vial, 15 mg/vial and 20 mg/vial Dose: 40 mg dose subcutaneously times one by physician followed by 10 mg to 30 mg daily	Orthographic similarities: The first letter 'S' can appear like the first letter 'G' when scripted, both names contain the letter 'v' in the same letter position and end with the upstroke/cross-stroke letter 't'. Overlapping product characteristics: Numeric overlap in doses of '10' mg versus mL, Dosage form: Lyophilized Powder for Injection versus Injection	Orthographic differences in the names, along with variations in product characteristics minimize the potential for confusion. Orthographic differences: There is an upstroke letter 'd' in the fourth letter position of Gadavist not present in the name Somavert that provides orthographic distinction. Differentiating product characteristics: Multiple strength versus singe strength availability Frequency of administration: Once daily versus one time use prior to imaging procedure
22	**Ultravist** (Iopromide) Injection Strength: 150 mg/mL provides 311.7 mg/mL iopromide, 240 mg/mL provides 498.72 mg/mL iopromide, 300 mgI/mL provides 623.4 mg/mL iopromide, 370 mg/mL provides 768.86 mg/mL iopromide. Dose: 3 mL to 200 mL intravenous	Orthographic similarities: There is an upstroke letter 't' versus 'd' in the third letter position of the names and both names end with the letters 'avist' versus 'ovist' Overlapping product characteristics: Dosage form: Injection Route of administration: Intravenous Both products are imaging agents Potential numeric overlap in doses of 1 mL to 14 mL	Orthographic differences in the names, along with variations in the strength minimize the potential for confusion. Orthographic differences: The first letter 'U' appears different than the first letter 'G' and there is an upstroke letter 'l' in the second letter position of Ultravist that is not present in Gadavist. Differentiating product characteristics: Strength: Multiple strength versus one strength availability with no numeric overlap in strength between the two products.

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/s/

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