CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-398

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO22, Mail Stop 4447)

DATE RECEIVED: July 26, 2006	**DESIRED COMPLETION DATE:** October 20, 2006	**OSE REVIEW #:** 01-0219-1
DOCUMENT DATE: June 29, 2006	**PDUFA DATE:** December 29, 2006	

TO: Janice Soreth, M.D., Director
Division of Anti-Infective and Ophthalmologic Products

THROUGH: Nora Roselle, Pharm.D., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Laura L. Pincock, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: **Combigan**
(Brimonidine Tartrate and Timolol Ophthalmic Solution)
0.2%/0.5%

NDA #: 21-398

NDA SPONSOR: Allergan, Incorporated

RECOMMENDATIONS:

1. DMETS reverses its initial decision and does not recommend the use of the proprietary name, Combigan. This is considered a final decision.

2. DMETS recommends implementation of the label and labeling comments outlined in Section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name "Combigan" acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
White Oak 22, Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW:	August 22, 2006
NDA#	21-398
NAME OF DRUG:	Combigan (Brimonidine Tartrate and Timolol Ophthalmic Solution) 0.2%/0.5%
NDA HOLDER:	Allergan, Inc.

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

This review contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Infective and Ophthalmologic Products, for re-assessment of the proprietary name, Combigan, regarding potential name confusion with other proprietary and/or established drug names. DMETS completed a review of the proposed proprietary name, Combigan, in OSE Consult 01-0219 dated January 8, 2002, and had no objections to the use of the proprietary name, Combigan. DMETS also reviewed and commented on the container labels, carton, and insert labeling in that review. Subsequently, Allergan received an approvable letter for NDA #21-398 on March 14, 2005. New labels and labeling have not been submitted subsequent to the approvable letter, and the review division has informed DMETS that the sponsor says they will not be changed from that original submission. Therefore, DMETS will review the proposed name, Combigan, for a second time, and will re-review the container label, carton labels, and insert labeling.

PRODUCT INFORMATION

Combigan is a prescription ophthalmic solution which contains a combination of the active ingredients Brimonidine Tartrate 0.2% and Timolol Maleate 0.5%. Each of these components decreases elevated intraocular pressure. Combigan is a selective alpha-2 adrenergic agonist with a non-selective beta-adrenergic receptor blocking agent. Combigan is indicated for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled intraocular pressure. The recommended dose is one drop of Combigan in the affected eye(s) twice daily. If more than one topical ophthalmic product is to be used, the different products should be instilled at least 5 minutes apart. Combigan will be supplied as 5 mL, 10 mL, and 15 mL ophthalmic solution bottles. [redacted] Combigan should be stored between 15-25°C (59-77°F).

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Combigan to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies for each proposed name consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Combigan. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC has no objections to the tradename "Combigan" from a promotional perspective.

2. Since the last proprietary name review, the Expert Panel identified eight additional proprietary names that were thought to have the potential for look-alike or sound-alike confusion with Combigan. These products are listed in Table 1 (page 4), along with the dosage forms available and usual dosage.

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[1] MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

[4] Phonetic and Orthographic Computer Analysis (POCA)

[5] WWW location http://www.uspto.gov/tmdb/index.html.

[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: COMBIGAN: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Combigan	Brimonidine Tartrate/Timolol Maleate Ophthalmic Solution: 0.2%/0.5% 5 mL (in 10 mL bottle), 10 mL (in 10 mL bottle) 15 mL (in 15 mL bottle)	One drop in the affected eye(s) twice daily. If more than one topical ophthalmic product is to be used, the different products should be instilled at least 5 minutes apart.	N/A
ComBgen **Rx**	Cyanocobalamin/Folic Acid/Pyridoxine Tablets: 500 mcg/2.2 mg/25 mg 100 count bottle	Adults: One (1) tablet orally once daily or based on individual needs as directed by a healthcare provider.	LA/SA
Coumadin	Warfarin Sodium Tablets: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg Powder for Injection: 5 mg/vial	Adults: Initially, 5 mg orally or intravenously once daily, with dosage adjustments made according to INR results. If a rapid anticoagulant effect is required, an initial dose of heparin should be used and overlapped with warfarin for at least 4 days. The maintenance dosage of warfarin should be based on INR determinations.	LA/SA
Ambien **Ambien CR**	Zolpidem Tartrate Tablets: 5 mg, 10 mg Tablets Extended-release: 6.25 mg, 12.5 mg	Ambien: Adults: 10 mg orally immediately before bedtime. Do not exceed 10 mg/day. Lower initial dosages (i.e., 5 mg at bedtime) may be appropriate for some patients on concomitant CNS-depressant medications. Ambien CR: Adults: 12.5 mg orally immediately before bedtime. Do not exceed 12.5 mg/day. Lower initial dosages (i.e., 6.25 mg at bedtime) may be appropriate for some patients.	LA
[redacted]			
Cosmegen	Dactinomycin Powder for Injection: 500 mcg/vial	Adults: 12 mcg/kg/day intravenously for 5 days as a single agent or in combination with other chemotherapy agents or 500 mcg on days 1 and 2 as part of a combination regimen with other chemotherapeutic agents.	LA
Combizym	Pancreatin *Foreign (marketed in Austria and Finland)*	No information available.	LA/SA
Corlopam	Fenoldopam Mesylate Solution for Injection: 10 mg base eq. /mL 1 mL and 2 mL ampules	Adults: Initially, infuse at 0.1 mcg/kg/min intravenously and titrated upwards. In general, the initial dose should be titrated upward or downward no more frequently than every 15 minutes in increments of 0.05—0.1 mcg/kg/min. The dose should be titrated.	LA/SA
Lumigan	Bimatoprost Ophthalmic Solution: 0.03% (bottles of 2.5 mL, 5 mL, 7.5 mL	Instill 1 drop in the affected eye(s) once daily in the evening.	LA

*Frequently used, not all-inclusive
**LA (look-alike), SA (sound-alike)
***Name pending approval. Not FOI releasable**

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Because the first name review was conducted in early 2002 with a small number of participants, three studies were conducted within the Centers of the FDA for the proposed proprietary names to determine the degree of confusion of Combigan 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. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and an order for Combigan (see below) were written. These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, a verbal pharmacy order was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Combigan #1 Instill one drop into affected eye bid	"Combigan, Dispense Number 1, Instill 1 drop into the affected eye(s) bid"
Inpatient RX: Combigan 0.1 gtt affected eye bid	

2. Results for Combigan:

Two respondents from the verbal study identified the proprietary name as "Coumidan" and "Coumadan", which are similar to the marketed drug, Coumadin. Another respondent from the verbal study identified the proprietary name as [redacted], a [redacted]. One respondent from the written inpatient study identified the proprietary name as "Ambigan", which is similar to the marketed drug, Ambien. The remaining misinterpretations were misspelled/phonetic variations of the name, Combigan. See Appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Combigan, the primary concerns identified relating to look-alike and sound-alike confusion with Combigan are ComBgen, Coumadin, Ambien, [redacted] Combizym, Cosmegen, Corlopam, and Lumigan.

DMETS conducted prescription studies to simulate the prescription ordering process. One respondent from the written inpatient study identified the proprietary name as "Ambigan", which is similar to the marketed drug, Ambien. Two respondents from the verbal study identified the proprietary name as "Coumidan" and "Coumadan", which are similar to the marketed drug, Coumadin. Another respondent from the verbal study identified the proprietary name as [redacted] The remaining misinterpretations from the study were misspelled/phonetic variations of the name, Combigan.

Upon further analysis, the names Coumadin, Ambien, [redacted], Cosmegen, Corlopam and Combizym were not reviewed further because:

1. Coumadin and Ambien lack convincing look-alike/sound-alike similarities with Combigan, in addition to numerous differentiating product characteristics such as the dosage form, product strength, indication for use, route of administration, and frequency of administration.

2. [redacted]

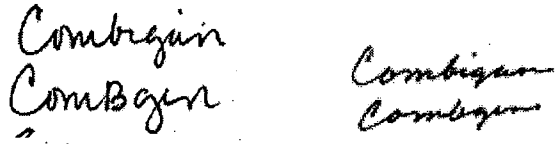
3. Cosmegen and Corlopam lack convincing look-alike/sound-alike similarities with Combigan, in addition to numerous differentiating product characteristics such as the dosage form, product strength, package size, indication for use, route of administration, and frequency of administration.

4. Combizym was identified as a proprietary name for a pancreatin product from Austria and Finland. No further information was available in widely used drug references such as Micromedex, Facts and Comparisons, and Lexi-Comp. Thus, Combizym will not be discussed further.

In review of the remaining names of concern, we have the following comments.

1. ComBgen was identified as a name with similar sound and appearance to Combigan. ComBgen is a prescription vitamin and mineral supplement containing Cyanocobalamin 500 mcg, Folic Acid 2.2 mg, and Pyridoxine 25 mg. ComBgen is usually prescribed as one tablet once daily or dosing may be based on individual needs as directed by a healthcare provider. ComBgen was first marketed in April 2004 by Ethex Corporation. Thus, ComBgen was not marketed at the time of our initial review for the proposed name, Combigan, in 2001.

The names ComBgen and Combigan look similar due to the identical beginning 'Com-' and the endings of both names may also look similar when scripted (-gan vs. -gen). The letter 'B' in ComBgen may look distinguishable if it is capitalized. However, prescribers do not always capitalize letters in the middle of a proprietary name when they write prescriptions. The lack of capitalization will make the names appear more similar (see below).



The two names may also sound similar due to the shared beginning. However, the letter 'g' in Combigan is usually pronounced with a hard letter sound (like the letter 'g' in gator), whereas the letter 'g' in ComBgen is usually pronounced with a soft sound (like the letter 'j' in jury) which may help to differentiate the two names. Thus, the two endings '-gan' and '–gen' usually sound distinguishable when spoken. However, the names can be pronounced differently by different people, and if either name is mispronounced, there is increased potential for confusion between the two names.

The products have differences, including dosage form (ophthalmic solution vs. oral tablet), product strength (0.2%/0.5% vs. 500 mcg/2.2 mg/25 mg), prescribed dose (one drop vs. one tablet), route of administration (ophthalmic vs. oral), dosing frequency (twice daily vs. once daily or as prescribed), package size (5 mL, 10 mL, or 15 mL vs. 100 count), and package configuration (dropper bottle vs. trade bottle).

Despite these differences, both products are single combination strengths. Thus a strength does not need to be indicated on a prescription for dispensing of the product which may increase the potential for confusion. Additionally, each product can be prescribed with ambiguous directions for use such as "as directed." Moreover, the amount to be dispensed for each drug can be written as #1 (i.e., 1 bottle, 1 month supply, etc.)

DMETS received drug usage data from the [redacted] database on the projected number of total prescriptions dispensed by retail pharmacies (chain, independent, food stores, mass merchandisers) in the United States (mail order excluded) for ComBgen. In 2005, a total of [redacted] prescriptions were dispensed for ComBgen. In 2006, the current year to date (July 2006), a total of [redacted] prescriptions were dispensed for ComBgen.[7] (This drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.) Thus, based on this data, ComBgen has familiarity in the marketplace. With the introduction of Combigan, practitioners may revert to the known drug (ComBgen) because of this product familiarity. Due to the similarity in spelling of these proprietary names and potential for prescriptions to be written as "Combigan/ComBgen, Dispense #1, as directed", DMETS is concerned with product confusion.

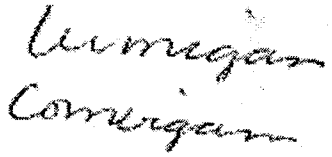
DMETS is not able to comment on the clinical significance should a patient receive the wrong drug product. However, should a patient use ComBgen rather than Combigan, their elevated intraocular pressure will not be adequately treated. In the reverse situation,

a patient will use unnecessary eye drops, and their anemia or vitamin deficiency will not be treated.

While there are product differences between ComBgen and Combigan, the names are so similar that the introduction of the name Combigan into the marketplace which already contains a product ComBgen is likely to be confusing. Therefore, as a result of strong look-alike and sound-alike properties, and the potential for harm should confusion occur between the names, DMETS does not recommend that the two names co-exist in the marketplace. DMETS recommends that the sponsor submit an alternate name to Combigan.

2. Lumigan was identified as a name with similar appearance to Combigan. Lumigan is a prescription eye drop for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension, an indication nearly identical to the proposed indication for Combigan. The recommended dose of Lumigan is one drop into the affected eye(s) once daily in the evening. Lumigan was approved on March 16, 2001.

The names Lumigan and Combigan look similar because the letter 'L' in Lumigan can resemble the letter 'C' in Combigan when scripted (see below). Additionally, both names contain the letter 'm' in the same position of each name and share the same ending '-gan'. The letter 'b' in Combigan may look distinguishable if it is scripted with a noticeable upstroke. However, should the upstroke from the letter 'b' be overlooked, the potential for confusion between the two names is increased.



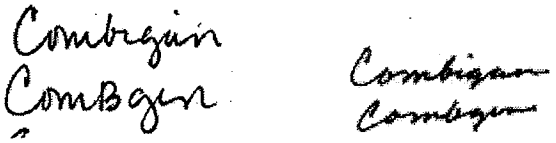
Additionally, Lumigan and Combigan share many product similarities, including dosage form (ophthalmic solution), prescribed dose (one drop), route of administration (ophthalmic), indication (elevated intraocular pressure), package size ([redacted] and 5 mL), and package configuration (ophthalmic bottle). The two products have two product differences such as; product strength (0.2%/0.5% vs. 0.03%) and dosing frequency (twice daily vs. once daily in the evening). However, although the product strengths are different, each product is only available in one strength, thus the strength can be omitted from a prescription which may increase the potential for confusion. Furthermore, if the names appear similar enough, the pharmacist may overlook the prescribed dosing frequency on a prescription (twice daily vs. once daily). Additionally, it is possible for prescriptions for Lumigan/Combigan to be written as "Lumigan/Combigan, Dispense 1 bottle, instill as directed." DMETS is not able to comment on the clinical significance should a patient receive the wrong drug product, although DMETS does note that the indications for both products are nearly identical. Therefore, as a result of look-alike properties, and the many product similarities between the two drug products, Lumigan and Combigan, DMETS does not recommend that the two names co-exist in the marketplace.

III. COMMENTS TO THE SPONSOR:

DMETS reverses its initial decision from 2002 and does not recommend use of the proprietary name, Combigan. In reviewing the proprietary name, Combigan, the primary concerns related to look-alike and sound-alike confusion with ComBgen and look-alike confusion with Lumigan.

A. ComBgen was identified as a name with similar sound and appearance to Combigan. ComBgen is a prescription vitamin and mineral supplement containing Cyanocobalamin 500 mcg, Folic Acid 2.2 mg, and Pyridoxine 25 mg. ComBgen is usually prescribed as one tablet once daily or dosing may be based on individual needs as directed by a healthcare provider. ComBgen was first marketed in April 2004 by Ethex Corporation. Thus, ComBgen was not marketed at the time of our initial review for the proposed name, Combigan, in 2001.

The names ComBgen and Combigan look similar due to the identical beginning 'Com-' and the endings of both names may also look similar when scripted (-gan vs. -gen). The letter 'B' in ComBgen may look distinguishable if it is capitalized. However, prescribers do not always capitalize letters in the middle of a proprietary name when they write prescriptions. The lack of capitalization will make the names appear more similar (see below).



The two names may also sound similar due to the shared beginning. However, the letter 'g' in Combigan is usually pronounced with a hard letter sound (like the letter 'g' in gator), whereas the letter 'g' in ComBgen is usually pronounced with a soft sound (like the letter 'j' in jury) which may help to differentiate the two names. Thus, the two endings '-gan' and '–gen' usually sound distinguishable when spoken. However, the names can be pronounced differently by different people, and if either name is mispronounced, there is increased potential for confusion between the two names.

The products have differences, including dosage form (ophthalmic solution vs. oral tablet), product strength (0.2%/0.5% vs. 500 mcg/2.2 mg/25 mg), prescribed dose (one drop vs. one tablet), route of administration (ophthalmic vs. oral), dosing frequency (twice daily vs. once daily or as prescribed), package size (5 mL, 10 mL, or 15 mL vs. 100 count), and package configuration (dropper bottle vs. trade bottle).

Despite these differences, both products are single combination strengths. Thus a strength does not need to be indicated on a prescription which may increase the potential for confusion. Additionally each product can be prescribed with ambiguous direction for use such as "as directed." Moreover, the amount to be dispensed for each drug can be written as #1 (i.e., 1 bottle, 1 month supply, etc.)

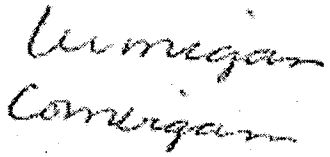
DMETS received drug usage data from the [redacted] database on the projected number of total prescriptions dispensed by retail pharmacies (chain, independent, food stores, mass merchandisers) in the United States (mail order excluded) for ComBgen. Thus, based on this data, ComBgen has familiarity in the marketplace. With the introduction of Combigan, practitioners may revert to the known drug (ComBgen) because of this product familiarity. Due to the similarity in spelling of these proprietary names and potential for prescriptions to be written as "Combigan/ComBgen, Dispense #1, as directed", DMETS is concerned with product confusion.

DMETS is not able to comment on the clinical significance should a patient receive the wrong drug product. However, should a patient use ComBgen rather than Combigan, their elevated intraocular pressure will not be adequately treated. In the reverse situation, a patient will use unnecessary eye drops, and their anemia or vitamin deficiency will not be treated.

While there are product differences between ComBgen and Combigan, the names are so similar that the introduction of the name Combigan into the marketplace which already contains a product ComBgen is likely to be confusing. Therefore, as a result of strong look-alike and sound-alike properties, and the potential for harm should confusion occur between the names, DMETS does not recommend that the two names co-exist in the marketplace. DMETS recommends that the sponsor submit an alternate name to Combigan.

B. Lumigan was identified as a name with similar appearance to Combigan. Lumigan is a prescription eye drop for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension, an indication nearly identical to the proposed indication for Combigan. The recommended dose of Lumigan is one drop into the affected eye(s) once daily in the evening. Lumigan was approved on March 16, 2001.

The names Lumigan and Combigan look similar because the letter 'L' in Lumigan can resemble the letter 'C' in Combigan when scripted (see below). Additionally, both names contain the letter 'm' in the same position of each name and share the same ending '-gan'. The letter 'b' in Combigan may look distinguishable if it is scripted with a noticeable upstroke. However, should the upstroke from the letter 'b' be overlooked, the potential for confusion between the two names is increased.



Additionally, Lumigan and Combigan share many product similarities, including dosage form (ophthalmic solution), prescribed dose (one drop), route of administration (ophthalmic), indication (elevated intraocular pressure), package size ([redacted] , and 5 mL), and package configuration (ophthalmic bottle). The two products have two product differences such as; product strength (0.2%/0.5% vs. 0.03%) and dosing frequency (twice daily vs. once daily in the evening). However, although the product strengths are different, each product is only available in one strength, thus the strength can be omitted from a prescription which may increase the potential for confusion. Furthermore, if the names appear similar enough, the pharmacist may overlook the prescribed dosing frequency on a prescription (twice daily vs. once daily). Additionally, it is possible for prescriptions for Lumigan/Combigan to be written as "Lumigan/Combigan, Dispense 1 bottle, instill as directed." DMETS is not able to comment on the clinical significance should a patient receive the wrong drug product, although DMETS does note that the indications for both products are nearly identical. Therefore, as a result of look-alike properties, and the many product similarities between the two drug products, Lumigan and Combigan, DMETS does not recommend that the two names co-exist in the marketplace.

Additionally, DMETS reviewed the labels and labeling from a safety perspective. DMETS has identified several areas of improvement, which might minimize potential user error.

C. GENERAL COMMENTS

1. The draft container label and carton labeling were submitted in black and white color and not submitted in a formatted layout. Thus, it is not possible to fully assess the safety of the

labels because the information provided does not reflect the presentation that will actually be used in the marketplace. Please forward copies of the revised labels in color and reflective of the presentation that will actually be used in the marketplace when they are available.

2. Ensure that the established name is at least one-half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2) on all labels and labeling. Increase the overall prominence of the proprietary name, established name, and strength.

3. We recommend that the established name appear beneath the proprietary name and that the forward slash between the two ingredients be replaced by the word "and".

D. CONTAINER LABELS: ([redacted] 5 mL, 10 mL, 15 mL)

1. We recommend that the "Rx only" statement appear on the principal display panel.

2. We recommend that the net quantity statement appear away from the product strength and have less prominence to decrease the potential for confusion.

3. We recommend that the word "DOSAGE" be changed to "USUAL DOSAGE" to be in accordance with 21 CFR 201.55.

E. CARTON LABELING: ([redacted] 5 mL, 10 mL, 15 mL)

See General Comments A1 through A3.

F. INSERT LABELING

1. See General Comment A3.

2. The insert labeling includes the abbreviations "BID" (two times a day), "TID" (three times a day), "IOP" (intraocular pressure), and "LDPE" (low-density polyethylene) which are not defined in the labeling. Post-marketing experience has demonstrated that such abbreviations can be misinterpreted and may lead to medication errors. Many prescribers use the abbreviations seen in approved labeling on their prescription orders. To minimize misinterpretations, FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols in their prescribing. [redacted] Thus, we request that the Divisions not approve or use such abbreviations in their labels and labeling.

3. PRECAUTIONS section, General sub-section

Appears This Way
On Original

NDA # 21-398
OSE Consult 01-0219-1

Appendix A: Combigan

Outpatient	Voice	Inpatient
Combigen	Combigan	Combigan
Combigan	Combigan	Combigan
Combigan	[redacted]	Combigan
Combigan	Compagan	Comsbigan (Connbigan)
Comsbigan	Compadan	Combizán
Combigan	Combigan	Combigan
Combigan	Coumadan	Comtergan
	Combigan	combegan
	Compigan	Combigan
	Conbigan	Combigan
	Comvigan	Comlagan
	Coumidan	Comtigen
	Combagen	Combigan
		Combegan
		Combigan
		Combigan
		Comtargan
		Comtagan
		Ambigan
		Combegan
		Compigan

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/s/

Nora L. Roselle
11/20/2006 01:04:34 PM
DRUG SAFETY OFFICE REVIEWER
Nora Roselle signing for Laura Pincock in her absence

Carol Holquist
11/20/2006 01:11:46 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: 10/27/01	**DUE DATE:** 1/7/02	**ODS CONSULT #:** 01-0219

TO: Jonca Bull, M.D.
Acting Director, Division of Anti-Inflammatory Analgesic, and Ophthalmologic Drug Products
HFD-550

THROUGH: Mike Puglisi
Project Manager, Division of Anti-Inflammatory Analgesic, and Ophthalmologic Drug Products
HFD-550

PRODUCT NAME: **Combigan** (Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution) **NDA#: 21-398**	**NDA SPONSOR**: Allergan, Inc.

SAFETY EVALUATOR: Nora Roselle, Pharm.D.

SUMMARY: In response to a consult from the Division of Anti-Inflammatory Analgesic, and Ophthalmologic Drug Products (HFD-550), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Combigan" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:
DMETS has no objection to the use of the proprietary name "Combigan". This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names from the signature date of this document. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

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HFD-400; Rm. 15B32
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PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 7, 2002

NDA NUMBER: 21-398

NAME OF DRUG: Combigan
(Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution)

NDA HOLDER: Allergan, Inc.

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

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Inflammatory Analgesic, and Ophthalmologic Drug Products (HFD-550) for assessment of the tradename "Combigan", regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION

Combigan is an ophthalmic solution which contains a combination of the active ingredients brimonidine tartrate 0.2% and timolol 0.5%. Each of these components decreases elevated intraocular pressure. Combigan is a selective alpha-2 adrenergic agonist with a non-selective beta-adrenergic receptor blocking agent, and has a rapid onset of action. Combigan is indicated for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension [redacted] Combigan is to be marketed as a prescription drug product. The recommended dose is one drop of Combigan in the affected eye(s) twice daily. Combigan is contraindicated in patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock, [redacted] or hypersensitivity to any component of this medication. Combigan will be supplied as [redacted], 5 mL, 10 mL, and 15 mL sterile, ophthalmic solution bottles.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to Combigan to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS)[4] was also conducted. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An Expert Panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies, consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Combigan". The expert panel is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Two product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with Combigan. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have concerns about the name with regard to promotional claims.

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).
[2] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.
[3] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.
[4] WWW location http://tess.uspto.gov/bin/gate.exe?f=tess&state=k0n826.1.1.
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at http://www.thomson-thomson.com.

TABLE 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Generic Name	Usual adult dose*	Other**
Combigan	Brimonidine Tartrate 0.2%/ Timolol 0.5% Ophthalmic Solution [redacted] 5 mL, 10 mL, 15 mL)	One drop in affected eye(s) twice daily	
Combivent	Ipratropium bromide and Albuterol sulfate, metered dose inhaler	2 inhalations four times a day	L/A, S/A
[redacted]			
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

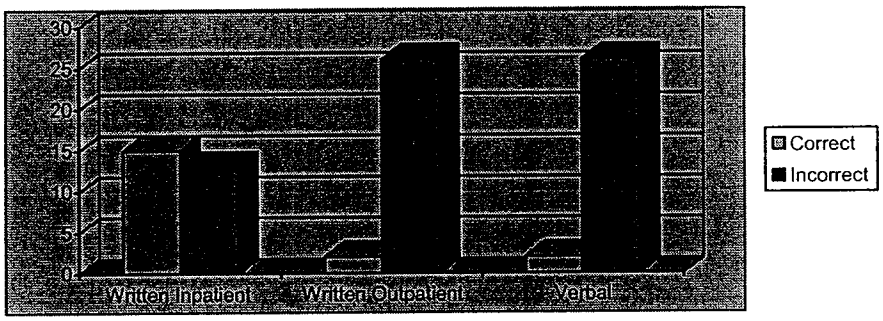
Three separate studies were conducted within FDA, to determine the degree of confusion of Combigan with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 113 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. A DMETS staff member wrote one inpatient and one outpatient order, each consisting of a combination of marketed and unapproved drug products and prescriptions for Combigan. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Inpatient Sample: Continue Combigan 1 gtt OD BID	*Outpatient*: Combigan Instill one drop into right eye once a day. Dispense one with no refills.
Outpatient Sample: Combigan 1 gtt OD BID #1	

2. Results

Results of these exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted Combigan	Incorrectly Interpreted
Written: Inpatient	34	28 (82%)	15 (54%)	13 (46%)
Outpatient	40	28 (70%)	2 (7%)	26 (93%)
Verbal: Outpatient	39	28 (72%)	2 (7%)	26 (93%)
Total	113	84 (74%)	19 (23%)	65 (77%)



Among the written outpatient prescriptions, 26 out of 28 (93%) respondents interpreted "Combigan" incorrectly. The majority of interpretations were phonetic/misspelled variations of the name, such as Combigar, Conergan, Conerigan, Conerigar, Conbigan, and Conbigar.

Among the written inpatient prescriptions, 13 out of 28 (46%) respondents interpreted "Combigan" incorrectly. Interpretations included Cambigan, Cambigam, Combigam, Cimbigan, Cambican, Cambizan, and Ambigan.

Among the verbal prescriptions, 26 out of 28 (93%) respondents interpreted "Combigan" incorrectly. Some of the incorrect interpretations included Condigan, Condigen, Comdigan, Condegan, Condagen, Convigan, and Comvigan.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Combigan, the primary concerns raised were related a sound-alike, look-alike name that already exists in the U.S. marketplace. *Combivent* was believed to be the most problematic in terms of potential medication error. Another drug name that was thought to have potential for medication error with Combigan was [redacted]

We conducted prescription studies to simulate the prescription ordering process. ***There was no confirmation that Combigan could be confused with Combivent*** [redacted] The results of the verbal and written analysis studies demonstrate that 19 of 84 (23%) participants interpreted the proprietary name Combigan correctly. The majority of the incorrect responses from the verbal and written studies were misspelled/phonetic variations of the drug name. These responses did not overlap with any existing approved drug products.

Combivent (ipratropium bromide and albuterol sulfate) is marketed as a prescription drug product. Combivent is a combination of the anticholinergic bronchodilator, ipratropium bromide, and the

beta $_2$ -adrenergic bronchodilator, albuterol sulfate. Combivent is supplied as a metered-dose inhaler indicated for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator. The dose of Combivent is two inhalations four times a day. Patients may take additional inhalations as required; however, the total number of inhalations should not exceed 12 in 24 hours. Combivent and Combigan can look and sound similar. Both tradenames contain three syllables and share the prefix "combi". However, there are distinguishing factors between Combivent and Combigan that may decrease the potential risk of medication errors. Differences between the two products include variations in indication, dosage form, route of administration, and dosing schedules. Combivent is a metered dose inhaler indicated in the treatment of COPD. Combigan is an ophthalmic solution used in the treatment of glaucoma and ocular hypertension. Likewise, Combivent is usually routinely dosed as two oral inhalations four times a day, while Combigan is dosed as one drop in the affected eye(s) twice daily. Also, there are differences in the product names when they are written which help to distinguish the two drug names if the prescription were written as "use as directed #1". Combivent contains an upstroke letter "t" with three letters preceding the "t". Combigan, on the other hand, contains a downstroke letter "g" in the middle of the name and has two letters following. Each of these letter combinations helps to differentiate Combivent and Combigan when they are written.

Combivent Combigan

The Labeling and Nomenclature Committee reviewed [redacted] and Combigan can look alike when written, but because [redacted] the potential for error is low.

[redacted] Combigan

The proprietary name does not contain any USAN stems.

Even though there are existing tradenames that look and sound similar to Combigan, there are distinguishing factors among the existing tradenames and Combigan that decrease the potential for confusion.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the insert and carton labeling, and container labels of Combigan, DMETS has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user error. Draft carton and container labels (8/01) were submitted for review.

A. DRAFT CONTAINER LABELS: ([redacted] 5 mL, 10 mL, 15 mL)

1. We recommend that the "Rx only" statement appear on the principal display panel.

2. We recommend that the established name appear beneath the proprietary name and that the forward slash between the two ingredients be replaced by the word "and".

3. We recommend that the net quantity statement appear away from the product strength and have less prominence.

4. We recommend that the word "DOSAGE" be changed to "USUAL DOSAGE".

B. DRAFT CARTON LABELING: [redacted] 5 mL, 10 mL, 15 mL)

See comments above, as applicable.

Appears This Way
On Original

IV. RECOMMENDATIONS

DMETS has no objection to the use of the proprietary name, Combigan. This is considered a tentative decision and the firm should be notified that this name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names from this date forward.

DMETS recommends the above labeling revisions that might lead to safer use of the product.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, Project Manager, at 301-827-3231.

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Concur:

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/s/

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