# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPROVAL PACKAGE FOR:

## APPLICATION NUMBER
## 21-286

# Administrative Documents

## 13. PATENT INFORMATION

Relevant method of use, pharmaceutical composition, and active pharmaceutical ingredient (active entity) patent information for Benevas™ Tablets (olmesartan medoxomil) is provided on the following pages.

June 13, 2000

PATENT INFORMATION

| | |
|---|---|
| Patent Number: | 5, 616, 599 |
| Date of Expiration: | April 1, 2014 |
| Type of Patent: | Active Pharmaceutical Ingredient, Pharmaceutical Composition and Method of Use Patent |
| Patent Owner: | Sankyo Co., Ltd.<br>Tokyo, Japan |

Original Declaration:

The undersigned declares that Patent No. 5, 616, 599 covers the Active Pharmaceutical Ingredient (chemical entity), Pharmaceutical Composition and Method of Use Patent of Benevas™ Tablets as an oral antihypertensive agent. This product is the subject of this application for which approval is being sought.

SANKYO PHARMA INC.

By: Richard S. Barth

Richard S. Barth, Esq.

June 13, 2000

PATENT INFORMATION

| | |
|---|---|
| Patent Number: | 5, 925,664 |
| Date of Expiration: | March 16, 2015 |
| Type of Patent: | Method of Use Patent |
| Patent Owner: | Sankyo Co., Ltd.<br>Tokyo, Japan |

Original Declaration:

The undersigned declares that Patent No. 5,925,664 covers the Method of Use of Benevas™ Tablets Patent as an oral antihypertensive agent. This product is the subject of this application for which approval is being sought.

SANKYO PHARMA INC.

By: Richard S. Barth

Richard S. Barth, Esq.

## 14. PATENT CERTIFICATION

A patent certification is required to be included only with a 505(b)(2) application. Sankyo Pharma Inc. is submitting a full NDA and therefore, a patent certification is not included. The Patent Certification section has been omitted intentionally.

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 21-286 SUPPL #_____

Trade Name: Benicar Generic Name: olmesartan medoxomil Tablets

Applicant Name: Sankyo Pharma Inc. HFD # 110

Approval Date If Known:

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES (NCE) /_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X__/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

**NO**

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TQ THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data,

would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?
YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/
(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature Date
Title:
Cn JS RHPM 10/5/01

Signature of Office/ Date
Division Director

cc: Original NDA 21-286 Division File HFD-93 Mary Ann Holovac

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
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Raymond Lipicky
10/5/01 04:01:58 PM

## PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

| | | | |
|---|---|---|---|
| **NDA Number:** | 021286 | **Trade Name:** | BENICAR(OLMESARTAN MEDOXOMIL)5/10/20/40M |
| **Supplement Number:** | 000 | **Generic Name:** | OLMESARTAN MEDOXOMIL |
| **Supplement Type:** | N | **Dosage Form:** | |
| **Regulatory Action:** | OP | **COMIS Indication:** | TREATMENT OF HYPERTENSION |
| **Action Date:** | 7/25/00 | | |

**Indication # 1** hypertension

Label Adequacy: Inadequate for ALL pediatric age groups

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): The applicant has requested a waiver from the requirement to conduct studies in the pediatric population. Dr. Stockbridge from the Division believed that the indication qualifies for pediatric studies and therefore should not be granted a waiver. A Pediatric Written Request was issued to the sponsor on March 6, 2001, to give the firm an idea of the type of studies that could satisfy the Pediatric Rule and possibly obtain additional marketing exclusivity. Therefore, the Pediatric Rule requirements for this application will be deferred until March 6, 2005.

**Ranges for This Indication**

| Lower Range | Upper Range | Status | Date |
|---|---|---|---|
| 0 years | Adult | Deferred | |

Comments: Please see note above.

**This page was last edited on 10/4/01**

S

Signature

10/4/01

Date

# DIVISION OF CARDIO-RENAL DRUG PRODUCTS

***Clinical Review***

**NDA**: 21-286 CS-866 (Benevas) for hypertension

**Sponsor**: Sankyo Pharma Inc.

**Review date**: January 5, 2001

**Reviewer**: N. Stockbridge, M.D., Ph.D., HFD-110

/S/ 1/5/01

**Summary:** With this original NDA submission, the sponsor has requested a waiver from the requirement to conduct studies in the pediatric population.

The indication of hypertension clearly qualifies for pediatric studies and such studies have been formally requested for numerous antihypertensive agents. Thus, pediatric studies are needed for CS-866, and a waiver should not be granted. A written request should be made and a commitment to conduct such studies in a timely fashion should be made a condition of approval (Phase IV commitment).

**Distribution**: NDA 21-286

HFD-110/Project Manager

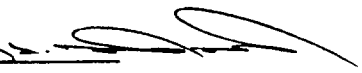
HFD-110/Stockbridge

**16. DEBARMENT CERTIFICATION**

June 30, 2000

CERTIFICATION PURSUANT TO 21 U.S.C. 306(K)(1)

Sankyo Pharma Inc. hereby certifies that it did not use and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

By: 

David L. Woodward, Ph.D.
Senior Vice President
Sankyo USA Development

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION **Public Health Service**
Division of Cardio-Renal Drug Products

**Memorandum**

**DATE** : October 16, 2001

**FROM** : Director, Division of Cardio-Renal Drug Products, HFD-110 /S/

**SUBJECT:** Approvable, olmesartan for hypertension, NDA 21-286, Sankyo

**TO** : Director, Office of Drug Evaluation I, HFD-100

As you remember from our meeting with the sponsor on October 3, 2001, you plan to have the carcinogenicity issue reviewed further and want another CAC meeting (at least). Consequently, the application cannot be approved until that occurs. However, as we discussed following the October 3 meeting, an approvable letter can be issued—olmesartan is approvable as evidenced by the attached marked –up package insert—once the animal studies are satisfactorily wrapped –up. Wrapping them up being our problem, the sponsor has done everything it can do (including having done more studies and gathering more historical control data.

Since the pharmacology issues must be resolved by Committee (and perhaps outside experts) by your edict, there cannot be a complete and final pharmacology review in the package. It is unknown what it should say the resolution is. Similarly, the pharmacology part of the Package Insert cannot be completed. As written, olmesartan would not be approvable, so how can such a label be forwarded under the guise of send in FPL.

Therefore it is not really possible to reliably mark-up the package insert.

It is attached, none-the-less, since (ignoring that as it now reads, olmesartan could not be approved) because it documents that olmesartan is approvable, once the pharmacology is resolved. The sponsor cannot resolve the pharmacology, only we can. Thus the sponsor cannot be expected to re-write the pharmacology parts of the label.

I suggest that the markup package insert not be sent to the sponsor, such sentences simply be omitted in the approvable letter. If that does not meet you standards, a standard approvable letter is also attached. Your choice.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 29, 2001

FROM: Robert Temple, M.D.
Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Olmesartan (Benicar, Sankyo, NDA 21-286)

TO: Raymond J. Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products, HFD-110

Apart from issues related to renal tumors, olmesartan appears effective and well-tolerated. The only side effect more common on olmesartan than placebo is dizziness. I do not believe there is a liver "signal." If you look at rate of 3x elevations you get:

| | **Plbo** | **2.5** | **5** | **10** | **20** | **40/80** | **10-80** |
|---|---|---|---|---|---|---|---|
| N | 555 | 282 | 884 | 527 | 566 | 435 | 1528 |
| % 3x ULN | 0.36 | 0 | 0.23 | 0.57 | 0.71 | 0 | 0.46 |

I believe there is no suggestion of an increased rate of 3x elevations.

The proposed dose is 20 mg, moving to 40 mg if needed, but I see little evidence that 40 mg has any role and even 20 mg does not seem clearly better than 10 mg.

Overall:

Trough values, all patients at 1° endpoint:

| Measure | | 2.5 (281) | 5 (598) | 10 (447) | 20 (436) | 40 (195) | 80 (188) |
|---|---|---|---|---|---|---|---|
| DBP | measured (-6.8) | -10.3 | -11.2 | -13.9 | -13.9 | -13.8 | -14.1 |
| | - plbo | 3.5 | 4.4 | 7.1 | 7.1 | 7.0 | 7.3 |
| | ABPM | 5.68 | 6.44 | 8.29 | 8.26 | --- | 7.24 |
| SBP | measured (-5.5) | -11.9 | -12.9 | -16.9 | -17.6 | -18.6 | -18.5 |
| | - plbo | 6.4 | 7.4 | 11.4 | 12.1 | 13.1 | 13.0 |

1. Even the small advantage on systolic BP for 40 over 20 is probably the result of much greater effect in blacks at 40 mg (but not seen at 80 mg).
2. 80 not >40 for anything.

3. 40 not >20 or 10 for DBP.
4. 40 very modestly >10/20 for SDP.
5. ABPM for DPB shows full effect at 10.

All in all, there's a good case for starting at 10 mg.

The PD section refers to data on AI infusions. Do we know what dose gives 24 hour inhibition >80, 90%?

It seems to me the elderly and people with marked renal or hepatic injury have of an enough increase in plasma levels to support a 50% dosage reduction.

Robert Temple, M.D.

cc:
Orig. NDA 21-286
HFD-110
HFD-110/Project Manager
HFD-101/R Temple
drafted:sb/10/23/01
final:sb/10/29/01
Filename:Olmesartan_MM_Oct01.doc

**RHPM Approval/Labeling Review**

Application: NDA 21-286
Benicar (olmesartan medoxomil)
5, 20, and 40 mg Tablets

Applicant: Sankyo Pharma Inc.

Date of FPL: April 6, 2002
Receipt of FPL: April 8, 2002
60 day due date: June 8, 2002

**Background:** An approvable letter, with marked-up draft labeling, was issued for NDA 21-286 on October 24, 2001. At the time the approvable letter was issued, the following still had to be resolved:

1) Genotoxiciy and Carcinogenicity Issues. The approvable letter stated that the Agency was concerned about the potential genotoxicity and carcinogenicity of olmesartan. Specifically, concerns included the interpretation of the *in vivo* mutation and clastogenicity assays and the numerical excess of renal tumors seen in the two-year rat carcinogenicity study. In the approvable letter, we asked the applicant to provide additional data and/or analyses of the currently available data.

*Resolution:*

Sankyo and the Agency agreed to the formation of a pathology working group (PWG) that would re-examine the relationship of olmesartan to the renal tumors seen in the two-year rat study. The PWG would be made up of members selected by the Agency as well as members chosen by the applicant.

The PWG met in November, 2001 and submitted their report to the Division in late December, 2001. The report confirmed the presence of renal tubular tumors in all groups of olmesartan-treated rats and the absence of such tumors in the concurrent control group. It also confirmed the absence of drug-associated renal tubular hyperplasia. The changes diagnosed as tubular cell hyperplasia by the original study pathologist (Sankyo) were considered by the PWG to be tubular hypertrophy, a non-proliferative change associated with chronic nephropathy.

The PWG was unable to determine, on the basis of morphology, whether the tumors seen in the olmesartan-treated rats were spontaneous or drug-induced. They did note, however, that on the basis of other factors ("lack of dose response and absence of increased incidence of hyperplastic lesions suggestive of preneoplastic changes") that "the few tubular cell tumors observed in this study" were not treatment related.

A second, full CAC meeting was convened on January 31, 2002 to review the genotoxic and carcinogenicity data and analyses. Sankyo made a presentation in which they concluded that "the few tubular cell tumors observed in the rat study are not related to treatment with olmesartan because of the absence of hyperplastic lesions suggestive of preneoplastic changes, the relatively low incidence of tumors, the lack of statistical significance, and the lack of a dose-response." They also claimed that "there was no relationship between renal tumors and chronic nephropathy, and a lack of genotoxicity in the kidney as determined by kidney Comet and MutaMouse studies."

After internal discussions, the CAC voted 16 – No, 1- Yes, and 3 – Uncertain to the question: Does the olmesartan-renal tumor association observed in the 2-year study in the Fischer 344 rat provide evidence of carcinogenic potential sufficient to label that study positive?

Comments from the majority of Committee members indicated that they based their decision to vote no because of the lack of proliferative lesions (hyperplasia), the absence of a dose relationship, and the absence of statistical significance to the tumor findings. Moreover, 3 out of the 4 members who voted yes or uncertain, noted that they did not believe this drug poses a risk for humans.

2) Removal of the word "Opadry" from the immediate carton and container labels. The approvable letter stated that the word "Opadry" be deleted from the immediate carton and container labels; it would be permissible to list all the specific components of Opadry in the alphabetical list of inactive ingredients stated on the label. Another option is to delete all reference to all inactive ingredients in the carton and container labels.

*Resolution*:

The applicant submitted draft carton and container labels on February 13, 2002 in which all inactive ingredients were removed. Dr. Srinivasachar said they were acceptable. The final carton and container labels (submitted April 6, 2002) are consistent with the approvable letter and have no mention of any inactive ingredients.

3) Blister and Blister Carton Labels and Shipping Labels. The approvable letter stated that blister and blister carton labels should be submitted for review; a sample of the label that will be used for shipping the bulk tablets for packaging from Germany to the United States should be supplied.

*Resolution:*

The applicant submitted, on February 13, 2002, blister and blister carton labels and bulk shipping labels. Dr. Srinivasachar said they were acceptable. The final (submitted April 6, 2002) blister and blister carton labels and bulk shipping labels were consistent with the February 13, 2002 submission.

4) Final Printed Labeling

*Resolution:*

After the full CAC deemed that olmesartan medoxomil was not a potential human carcinogen, Dr. Resnick revised the **Carcinogenesis, Mutagenesis, and Impairment of Fertility** subsection and this revision was sent (on February 27, 2002) to the applicant. Sankyo agreed with the Division's changes to this subsection.

A telecon was held on March 7, 2002 to discuss other sections of the labeling. Shortly before the telecon began, a revision of the **Dosage and Administration** section was sent to the applicant. Dr. Throckmorton noted that this revision includes a provision for a lower starting dose for those patients that may be volume depleted or those patients that have impaired renal function. He said this change would make it more consistent with the **Dosage and Administration** sections of the other sartans. Dr. Throckmorton said that we believe a dose of 5 mg should be made available for these special populations. Sankyo said that a 5 mg dose was acceptable and they would make this strength available for marketing.

Dr. Temple noted that the applicant should revise, under **Clinical Trials**, the bar graph entitled "Dose-Response for BENICAR, Sitting Blood Pressure, Change from Baseline" and change it into a line graph. Dose-Response data from a meta-analysis of the trials should be generated to show placebo-subtracted lines (one each for systolic and diastolic blood pressures). Sankyo said they would revise the graph and asked if least square means could be used for statistical analysis of the data. Dr. Temple said this was acceptable.

The Agency and Sankyo also discussed changes to the **Clinical Pharmacology, Special Populations, Pharmacodynamics, Geriatric Use, Adverse Reactions**, and **How Supplied** sections of the labeling.

After several more minor revisions to the labeling by Sankyo and the Agency, (some in response to Dr. Andy Haffer's memo of March 22, 2002) we agreed that their faxed submission of April 5, 2002 was acceptable and that final printed labeling could be submitted.

Sankyo sent in FPL on April 6, 2002 (our receipt date is April 8, 2002). The FPL submitted was identical to what had been agreed to in the labeling negotiations. However, during the internal routing process, Dr. Temple and the reviewers of the application requested several additional changes to be made at the next printing. These were as follows:

Dr. Resnick (after receiving labeling suggestions from the Office Pharmacologist, Dr. Jeri El-Hage) recommended the following changes to the Pharmacology sections of the labeling:

1. Under **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**, please delete from the second paragraph the words [redacted]

2. Under **OVERDOSAGE**, please delete the second paragraph, which makes reference to studies in mice, rats, and dogs.

3. Under **WARNINGS, Fetal/Neonatal Morbidity and Mortality**, the next to last sentence notes, among other things, drug associated "delays in developmental milestones." This sentence should be modified to specify which *developmental milestones* were delayed.

4. [redacted]

Drs. Temple, Throckmorton, and Stockbridge also suggested the following changes to the **ADVERSE REACTIONS** section of the labeling:

1. Under **ADVERSE REACTIONS**, 3rd paragraph, the adverse events of "inflicted injury" and "upper respiratory tract infection" should be deleted.

2. Under **ADVERSE REACTIONS,** the listing of "other (potentially important) adverse events....in controlled or open-label trials" should be changed to:

*Body as a Whole:* chest pain, peripheral edema
*Central and Peripheral Nervous System:* vertigo
*Gastrointestinal:* abdominal pain, dyspepsia, gastroenteritis, nausea
*Heart Rate and Rhythm Disorders:* tachycardia
*Metabolic and Nutritional Disorders:* hypercholesterolemia, hyperlipemia, hyperuricemia
*Musculoskeletal:* arthralgia, arthritis, myalgia
*Skin and Appendages:* rash

In telephone conversations between myself and Dr. James Molt of Sankyo on April 23 and 24, 2002, it was agreed that the above labeling changes would be made at the next printing and submitted as a supplement to this application.

**Comments/Recommendation:** There are no other unresolved issues for this NDA. An approval letter will be drafted for Dr. Temple's signature.

Edward Fromm
Regulatory Health Project Manager

ef/4-25-02

RHPM NDA Overview
October 17, 2001

**NDA 21-286** Benicar (olmesartan medoxomil)
5, — 20, and 40 mg Tablets

**Sponsor:** Sankyo Pharma

**Classification:** 1 S

**Indication:** Hypertension

**Date of Application:** July 25, 2000
**Date of Receipt:** July 25, 2000
**User Fee Goal Date:** October 25, 2001

**Background**

Sankyo has submitted this NDA for olmesartan medoxomil, an angiotensin II receptor antagonist, for the treatment of hypertension. Studies for olmesartan medoxomil (formerly known as CS-866) were conducted under IND — IND — ' was initially submitted to the Division on May 2, 1995.

There were 7 placebo-controlled studies and four active comparator studies that were submitted to support the safety and efficacy of the drug. Studies 866-204, 305 and 306 were considered pivotal for efficacy.

At the time of NDA submission, the applicant was planning to market two strengths of the tablets, 20 and 40 mg. The Division, however, believed that a 5 mg strength should also be available for special populations. In teleconferences on December 7, 2000 and March 7, 2001 the Division received a commitment from Sankyo to market the 5 mg strength. Subsequent to these discussions, Sankyo submitted CMC and bioequivalence data to support the new strength and also submitted revised draft labeling that includes references to the 5 mg tablet.

Olmesartan medoxomil is clastogenic in most of the *in vitro* tests. Dr. Lipicky informed the sponsor at a February 16, 2000 meeting, that the Division was concerned about this finding and asked the sponsor to submit other animal data (e.g., carcinogenicity studies) to support the safety of the drug. The sponsor submitted 3 carcinogenicity studies with the original NDA. These studies were reviewed by the Division and presented before the Executive CAC on March 20, 2001. The committee expressed concern that there were nominal (but not statistically significant) increases in tumor development in the renal tubules of female and male rats. They asked the Division to follow-up on these concerns by reviewing group incidences of hyperplasia for all organs where a nominal increase in tumor incidence was observed. The Executive CAC asked that, where incidences of the same cell type are found to be increased, the Division should ask the sponsor for historical control data for each of these tumors. When the data from the sponsor was received and reviewed by the Division, it should be presented before the full CAC.

The historical control data from the sponsor was received on March 30, 2001. Dr. Lipicky said this information constituted a major amendment to the NDA and consequently the 10-month review clock was extended.

A full CAC meeting was held on May 4, 2001 with the sponsor present. Sankyo argued that the genotoxicity profile for olmesartan was similar to other sartans and that long and short-term carcinogenicity studies were negative for the compound. Several CAC members questioned the sponsor's claim that the renal hyperplasia seen in the mouse and rat studies were not neoplastic. Some felt that an independent panel, such as the NCTR (National Center for Toxicological Research) or NTP (National Toxicology Program), could read the kidney slides and provide a distinction between tubular hyperplasia, adenoma, and carcinomas. In the end, the CAC voted 12 to 8 that the 2-year Fisher 344 rat study did provide evidence of olmesartan causing a positive carcinogenic response.

At an internal meeting on May 17, 2001, Drs. DeGeorge, Resnick, and Jagadeesh presented the CAC's findings to Dr. Temple. Dr. DeGeorge noted that the genotoxicity seen with olmesartan appeared to be much greater than other sartans. In addition, renal adenomas/carcinomas were seen in the 2-year rat study (at levels above the background rate) as well as significant kidney hyperplasia. Hyperplasia was also present in the kidneys of mice in the short-term mouse carcinogenicity assay. Dr. DeGeorge expressed concern with these findings because they are inconsistent with the carcinogenic profile of other sartans approved to date.

The pharmacology team believed that an independent reading of the kidney slides by NTP or NCTR and/or having them step sectioned and read blinded could help differentiate hyperplasia from adenomas and/or carcinomas. The problem with this approach is that the proposed tests might not be completed before the July action date.

Dr. Temple said that, short of other tests being submitted before the action date, he would most likely recommend a not-approvable action for the application. He noted that olmesartan medoxomil offered no significant advantage over existing sartan products and that the apparent genotoxic/carcinogenic effects of the drug were troubling.

Sankyo met with the Agency on May 30, 2001 to discuss the genotoxic/carcinogenic issues. At the meeting the firm agreed to do the following additional tests to further determine the extent of the genotoxic and carcinogenic properties of the drug:

- A re-reading of the rat carcinogenicity study kidney slides by a National Toxicology Program (NTP) pathologist. The idea is to confirm that the adenomas seen so far are in fact tumors and not hyperplasia and that none of the hyperplasias that were identified are adenomas. Additionally, the re-reading of the slides may be able to differentiate hypertrophy from hyperplasia.
- Step sectioning the rat kidney tissues and reading them in a blinded manner.
- PCNA (Positive Cell Nuclear Antigen) histochemical evaluation on the kidney slides that may show quantitative differences between hyperplasia and hypertrophy.
- Comet Assay, which is a method to examine DNA damage. This test may provide additional information about the genotoxic potential of the drug.
- Submit the results of the third Muta-Mouse study to the Division. The Muta-Mouse study looked for mutations in intestinal tissue from the mouse.

Dr. Temple said that after the firm sends the slides to the NTP pathologist, they should acknowledge this in a letter to the Division. The Agency will classify this letter (when received by July 25, 2001) as a major amendment, which will extend the 12-month review clock by 3 months.

Sankyo, on July 3, 2001, sent a letter acknowledging that rat carcinogenicity slides had been sent to the NTP pathologist. The Division classified this letter a major pharmacology amendment and consequently the 12-month review clock was extended by 3 months to October 25, 2001.

After several internal meetings to discuss the test results that were submitted in accordance with the May 30, 2001 meeting, Dr. Temple informed the firm at a meeting on October 3, 2001, that the Agency was still concerned about the mutagenic and carcinogenic potential of the drug. He said that the Agency would like the CAC to re-review olmesartan in light of the test results recently submitted by the firm as well as mutagenic and tumor incidence data that are available of other sartans. Because the application has a PDUFA goal date of October 25, 2001, an approvable letter will be issued to the firm that will state that before approving olmesartan, the Agency will need to have further discussions with the firm and perhaps additional animal data to determine that the drug is not a potential human carcinogen.

Meetings

End-of Phase 2: May 14, 1997
Pre-NDA: October 27, 1998

**Review**

Medical

| | |
|---|---|
| Division Director: | Raymond Lipicky, M.D. |
| Labeling: | None; Dr. Lipicky suggested that marked-up draft labeling not be sent with the approvable letter because the pharmacology concerns with the drug have not been entirely resolved. In other words, our mark-up of the labeling would suggest that we know what the pharmacology section should say when in fact we have not resolved these issues. |
| Conclusion: | Approvable; the firm will need to fully address our concerns regarding the mutagenicity and carcinogenicity before approval can be granted. |
| Medical Reviewers: | Steven Rodin, M.D.<br>Shari Targum, M.D<br>Akinwole Williams, M.D. |
| Labeling: | Please see their July 9, 2001 review. |
| Conclusion: | "We estimate Benicar's therapeutic benefit to risk relationship as being acceptable for the proposed patient population...We recommend that Benicar be approved subject to establishing that Benicar is not mutagenic and that other safety issues that may be of concern are indicated in the package insert." |
| Secondary Medical: | Norman Stockbridge, M.D., Ph.D. |
| Labeling: | Dr. Stockbridge made several revisions and editorial changes to the labeling. He suggested that the sponsor address the following: (1) dose-response graph should show placebo-corrected data for all doses assessed, and (2) twice-daily use should be discouraged as not useful. |
| Conclusion: | "Olmesartan is clearly effective as a one-daily antihypertensive." He notes that clastogenicity, mutagenicity, and carcinogenicity data suggest plausibly real findings; however, these findings appear do not be |

appreciably different from other members of the angiotensin receptor blocker class.

Statistical

Statistical Reviewer: James Hung, Ph.D.

Labeling: None

Conclusion: "The three studies (866-204, 305 and 306) show that olmesartan at a daily dose greater than 5 mg resulted in a statistically significant greater reduction in blood pressures as compared to placebo. Based on the results of Studies 866-204 and 866-305, there is a positive dose response indicating that the greater the daily dose the greater blood pressure decreases are. Increases in blood pressure reduction appear to start leveling off at some dose in the range of 25 to 52 mg."

Biopharmaceutics

Reviewer: Sayed Al-Habet, Ph.D.

Labeling: Dr. Al-Habet, said that under **CLINICAL PHARMACOLOGY, Pharmacokinetics,** first sentence, the word " [redacted] " should be deleted.

Conclusion: approvable; Dr. Al-Habet suggested that a lower strength of the drug be available for renally and hepatically impaired patients.

Chemistry

Reviewer: Florian Zielinski, Ph.D.

Labeling: Dr. Zielinski suggested that under **DESCRIPTION,** last sentence of the last paragraph, the phrase "Opadry containing" should be deleted and the components of Opadry should merged into the alphabetical listing of inactive ingredients of the tablet core.

The firm should remove the name "Opadry" from all carton and container labels. Dr. Zielinski noted that the firm may choose one of the following two options:

1. Delete all reference to all inactive ingredients in the container labels and carton labels – or –
2. List the specific components of Opadry in the alphabetical list of inactive ingredients stated on the label but delete reference to Opadry per se.

Dr. Zielinski suggested that Sankyo supply a sample of the label that will be used on the container for shipping the bulk tablets from Germany to the United States for packaging. Labeling for blisters and blister cartons are also needed.

CGMP Inspections: Acceptable, September 26, 2000

Methods Validation: Pending

Environmental Assessment: Exclusion granted

Conclusion: approvable

Secondary Pharmacology:

Reviewer: Charles Resnick, Ph.D.

Conclusion: Approvable with conditions, see Dr. Resnick's October 17, 2001 Secondary Pharmacology Review. Dr. Resnick believes that because the

pharmacology issues with olmesartan have not been resolved, the marked-up draft labeling should not be included with the approvable letter.

| | |
|---|---|
| Pharmacology (Draft) | |
| Reviewer: | Gowra Jagadeesh, Ph.D. |
| Labeling: | See Dr. Jagadeesh's October 17, 2001 pharmacology review for his suggested labeling changes. |
| Conclusion: | Approvable with recommended labeling changes |
| Statistics (preclin): | Roswitha Kelly, M.S. |
| Conclusion: | Please see Ms. Kelly's March 3, and October 1, 2001 reviews. |
| Safety Update: | Included in medical review. |
| Patent info: | Included in package |
| Pediatric info: | Deferral, the firm will have until March 6, 2005 to complete the pediatric studies. |
| DSI: | DSI audits were not requested by the Division; however, DSI conducted inspections on their own and found no major deficiencies. |

Debarment Certification: Included in package

Exclusivity Summary: Included in package

Financial Disclosure: The sponsor denies having any inappropriate financial arrangements (see Dr. Stockbridge's Secondary Medical Review).

OPDRA Tradename Review: The applicant's proposed tradename of Benevas was found unacceptable by OPDRA on August 24, 2000; their alternative name of Benicar was to found to be acceptable.

Comments: Per Dr. Lipicky's instructions, I will draft two versions of an approvable letter (one with and one without marked-up draft labeling) for Dr. Temple's signature.

/S/

Edward J. Fromm

dr-ef-10-17-01

16 pages redacted from this section of the approval package consisted of draft labeling

**Office of Drug Safety**

# Memo

**To:** Douglas Throckmorton, M.D.
Acting Director, Division of Cardio-Renal Drug Products
HFD-110

**From:** Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400

**Through:** Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400

**CC:** Edward Fromm
Project Manger
HFD-110

**Date:** March 15, 2002

**Re:** ODS Consult 01-0041-2; Benicar (Olmesartan Medoxomil Tablets ) 5 mg, 20 mg, 40 mg; NDA 21- 286

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This memorandum is in response to a February 26, 2002 request from your Division for a re-review of the proprietary name, Benicar.

DMETS has not identified any additional proprietary or established names that have the potential for confusion with Benicar since we conducted our initial review on March 12, 2001 (OPDRA consult

01-0041) that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

APPEARS THIS WAY
ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
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Alina Mahmud
3/21/02 03:36:30 PM
PHARMACIST

Carol Holquist
3/22/02 07:21:14 AM
PHARMACIST

**Office of Post-Marketing Drug Risk Assessment (OPDRA)**

# Memo

**TO:** Raymond Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products
HFD-110

**FROM:** David Diwa, Pharm.D.
Safety Evaluator, Office of Post-Marketing Drug Risk Assessment
HFD-400

**THROUGH:** Jerry Phillips, R.Ph.
Associate Director, Office of Post-Marketing Drug Risk Assessment
HFD-400

**CC:** Edward Fromm
Project Manger
HFD-110

**DATE:** October 11, 2001

**RE:** OPDRA Consult 01-0041, Benicar (olmesartan medoxomil) NDA 21-286

---

This memorandum is in response to a request from your Division on September 7, 2001 for a re-review of the proprietary name, Benicar. The expected approval date of this application is November 15, 2001. OPDRA has not identified any safety concerns that would render the proposed name objectionable. Therefore, we have no objections to the use of this proprietary name.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3231.

APPEARS THIS WAY
ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
---
David Diwa
10/12/01 09:11:08 AM
PHARMACIST

Jerry Phillips
10/12/01 10:44:11 AM
DIRECTOR

**CONSULTATION RESPONSE**
**Office of Post-Marketing Drug Risk Assessment**
**(OPDRA; HFD-400)**

| **DATE RECEIVED:** 2/12/01 | **DUE DATE:** 3/16/01 | **OPDRA CONSULT:** 01-0041 |
|---|---|---|

**TO:**

Raymond Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products
HFD-110

**THROUGH:**

Edward Fromm
Project Manager, Division of Cardio-Renal Drug Products
HFD-110

| **PRODUCT NAME:**<br><br>Benicar (olmesartan medoxomil tablets),<br>5 mg, 20 mg, and 40 mg<br><br>**NDA #:** 21-286 | **MANUFACTURER:** Sankyo Pharma Inc. |
|---|---|

**SAFETY EVALUATOR:** Jennifer Fan, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Cardio-Renal Drug Products (HFD-110), OPDRA conducted a review of the proposed proprietary name "Benicar" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

**OPDRA RECOMMENDATION:**
OPDRA has no objection to the use of the proprietary name, "Benicar".

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
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/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☒ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approval of other proprietary names/NDA's from this date forward.

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: 301-827-3242
Fax: 301-480-8173

/S/

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

**HFD-400; Rm. 15B03**
**Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** March 12, 2001

**NDA NUMBER:** 21-286

**NAME OF DRUG:** Benicar (olmesartan medoxomil tablets), 5 mg, 20 mg, and 40 mg

**NDA HOLDER:** Sankyo Pharma Inc.

## I. INTRODUCTION:

This consult was written in response to a request from the Division of Cardio-Renal Drug Products (HFD-110) for assessment of the tradename "Benicar". "Benicar" is the second proprietary tradename that was submitted to the Agency by the sponsor after OPDRA recommended to not accept the sponsor's original tradename "Benevas".

"Benevas" was reviewed by the Labeling and Nomenclature Committee (LNC) on April 28, 1999 and was found acceptable. However, since "Benevas" was not reviewed by OPDRA, the Division of Cardio-Renal Drug Products requested an OPDRA consult (Consult #00-0207) for "Benevas" on August 2, 2000. On August 9, 2000, OPDRA's Expert Panel Discussion (EPD) decided that "Benevas" was too similar to
OPDRA.

The Division of Cardio-Renal Drug Products was informed by e-mail on August 24, 2000 of OPDRA's recommendation to not accept the proprietary name "Benevas".

PRODUCT INFORMATION

"Benicar" is a prodrug that is hydrolyzed to olmesartan during absorption in the gastrointestinal tract. Olmesartan is a selective $AT_1$ subtype angiotensin II receptor antagonist. "Benicar" is indicated for the treatment of hypertension. It is supplied as 5 mg, 20 mg, and 40 mg tablets.

## II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to "Benicar" 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

[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 Company Inc, 2000).
[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.
[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA 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 OPDRA to gather professional opinions on the safety of the proprietary name "Benicar". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA 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.

Several product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with "Benicar". These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage. When given a poll of EPD regarding the similarity between *Mevacor* and "Benicar", three out of five people viewed the two names as similar.

DDMAC did not find the proprietary tradename, "Benicar", misleading.

Table 1

| **Product Name** | **Dosage form(s), Generic name** | **Usual adult dose*** | **Other**** |
|---|---|---|---|
| **Benicar** | olmesartan medoxomil tablets<br>(Anit-hypertensive – Rx)<br><br>Tablet: 5 mg, 20 mg, and 40 mg | 20 mg once a day. | |
| Mevacor | Lovastatin<br>(Anti-hyperlipidemic – Rx)<br><br>Tablet: 10 mg, 20 mg, and 40 mg | 10 mg – 80 mg once or twice a day. Starting dose: 20 mg once a day. | S/A, L/A per OPDRA |
| Amicar | Aminocaproic Acid<br>(Hemostatic Agent – Rx)<br><br>Injection: 250 mg/mL<br>Syrup: 250 mg/mL<br>Tablet: 500 mg | 5g orally or IV initially, then 1.25 g per hour. No more than 30 g a day. | S/A, L/A per OPDRA |
| Betatar Gel Shampoo | Coal Tar Solution<br>(Anti-psoriasis – OTC)<br><br>Shampoo: 5% | Apply weekly. | S/A per OPDRA |
| Vaniqa | Eflornithine HCl<br>(Reduce unwanted facial hair – Rx)<br><br>Cream: 13.9% | Apply twice a day. | S/A per OPDRA |
| Bethanechol Chloride | Brand name: Urecholine<br>(Urinary Cholinergic – Rx) | 10 to 50 mg three to four times a day. | S/A per OPDRA |

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

| Product Name | Dosage form(s), Generic name | Usual adult dose* | Other** |
|---|---|---|---|
| Benicar | olmesartan medoxomil tablets<br>(Anit-hypertensive – Rx)<br><br>Tablet: 5 mg, 20 mg, and 40 mg | 20 mg once a day. | |
| | Tablet: 5 mg, 10 mg, 25 mg, and 50 mg | | |
| Zinecard | Dexrazoxane HCl<br>(Anti-neoplastic – Rx)<br><br>Powder for Injection, lyophilized: 250 mg, 500 mg (both 10 mg/mL reconstituted) | 500 mg/m$^2$ dexrazoxane slow IV push or rapid drip IV infusion from a bag. | S/A per OPDRA |
| Benecol | Plant Stanol Esters<br>(Dietary Supplement: lowers blood cholesterol – OTC)<br><br>Spread<br>Softgels: 500 mg | Spread: 3 servings a day.<br>Softgels: 3 capsules three times a day. | S/A, L/A per OPDRA |
| | | *Frequently used, not all-inclusive | **S/A(Sound-alike), L/A (Look-alike |

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

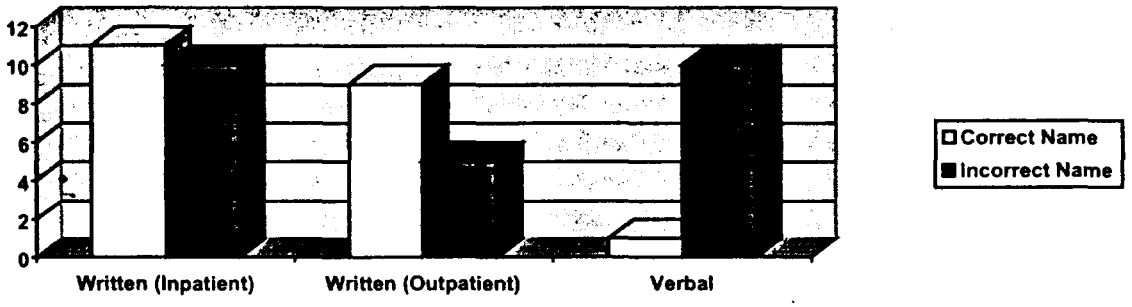
Studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of "Benicar" and with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 86 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote one inpatient prescription and one outpatient prescription, each consisting of a combination of marketed and unapproved drug products and prescriptions for "Benicar" (see below). These written prescriptions were optically scanned and one prescription was delivered via e-mail to each study participant. In addition, one OPDRA 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 e-mail.

| HANDWRITTEN PRESCRIPTIONS | VERBAL PRESCRIPTION |
|---|---|
| "BENICAR" | |
| *Inpatient:*<br>Benicar 20 mg po bid | *Outpatient:*<br>Benicar 20 mg, number 60, take 1 po bid. |
| *Outpatient:*<br>Benicar 20 mg<br>#60<br>Sig: 1 po BID | |

2. Results:

*Results of these exercises are summarized below:*

| Study | # of Participants | # of Responses (%) | Correctly Interpreted "Benicar" | Incorrectly Interpreted |
|---|---|---|---|---|
| Written: Inpatient | 28 | 21 (75%) | 11 (52%) | 10 (48%) |
| Outpatient | 28 | 14 (50%) | 9 (64%) | 5 (36%) |
| Verbal: Outpatient | 30 | 11 (37%) | 1 (9%) | 10 (91%) |
| Total | 86 | 46 (53%) | 21 (46%) | 25 (54%) |




Among the verbal outpatient prescription, 10 (91%) respondents interpreted "Benicar" incorrectly. From the written inpatient and outpatient prescriptions, there were more respondents who interpreted "Benicar" correctly; however, the number of respondents who interpreted "Benicar" incorrectly were almost equal to the number of respondents who interpreted the tradename correctly.

When examining the interpretations from the written inpatient and outpatient prescriptions, several respondents interpreted "Benicar" as *Bevicar* and *Benicor*. The "n" can sometimes be misinterpreted as a "v", and the "a" can be misinterpreted as an "o" when scripted. Among the intepretations from the voice outpatient prescription, respondents intepreted "Benicar" as *Benacor, Benacar, Benecar,* and *Benacard.* When "Benicar" is pronounced over the telephone, certain vowels can be hard to distinguish from each other, such as the "i" can be misinterpreted as an "e" or "a".

## C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Benicar", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. Such names are *Amicar, Betatar, Vaniqa, Zinecard, Benecol, Bethanechol, and Mevacor.*

*Amicar* is indicated for the treatment of excessive bleeding resulting from systemic hyperfibrinolysis and urinary fibrinolysis. *Amicar* and "Benicar" sound and look similar when pronounced and scripted. The "m" can be misinterpreted as an "n" when pronounced or an "en" when scripted. The capital "a" in *Amicar* can be scripted in a way to look like a "b". However, there are distinguishing factors between "Benicar" and *Amicar*, which may decrease the potential risk of medication errors. Even though both drug products are available in a tablet dosage form, they both have different strengths. *Amicar* is available as a 500-mg tablet while "Benicar" is available in 5 mg, 20 mg, and 40 mg. Also, the dosing directions are different between the two drug products. "Benicar" is taken once a day while *Amicar* is given 5 g orally or IV initially, then 1.25 g per hour.

*Betatar*, *Vaniqa*, and *Zinecard* also sound similar to "Benicar"; however the difference in dosage forms, strengths, and the directions of use between these products and "Benicar" would decrease the potential risk of medication errors. Please note that one respondent from the OPDRA study interpreted "Benicar" as *Benacard*, which sounds similar to *Zinecard*.

*Benecol* is an over-the-counter (OTC) dietary supplement, which claims to reduce cholesterol levels. The product is available as a spread and softgel (500 mg). *Benecol* sounds and looks very similar to "Benicar". In some instances, a prescriber may write an OTC medication on a prescription form. The patient, who may not know that *Benecol* is an OTC product, may submit the prescription to a pharmacy where "Benicar" may be dispensed. However, there are factors that would distinguish the two products. The *Benecol* SoftGel is only available in one strength while "Benicar" is available in more than one strength. The dosing schedules of the two products are also different. According to McNeil Consumer Healthcare, who manufactures *Benecol*, the softgels are currently available only through the Internet. These differences would decrease the potential risk of medication errors.

*Bethanechol* is indicated for the treatment of acute postoperative and postpartum nonobstructive (functional) urinary retention and neurogenic atony of the urinary bladder with retention. *Bethanechol* sounds similar to "Benicar". Both products are available as tablets and also have overlapping strengths. *Bethanechol* tablets are available in 5mg, 10 mg, 25 mg, and 50 mg while "Benicar" is available in 5 mg, 20 mg, and 40 mg. However, *Bethanechol* is usually taken three to four times a day while "Benicar" is taken once a day. Also, *Bethanechol* contains four syllables while "Benicar" contains three syllables. This difference in syllables can distinguish the two proprietary names from each other.

*Mevacor* is indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total-C and LDL-C to target levels. *Mevacor* sounds and looks similar to "Benicar". Both tradenames contain three syllables. The "v" in *Mevacor* can sound like an "n" over the telephone, and the "car" in "Benicar" can sound like "cor" *Mevacor*. From the outpatient verbal prescriptions in the OPDRA study, one respondent misinterpreted "Benicar" as *Benacor*. When the two tradenames are written in script, the "v" and "o" in *Mevacor* can be misinterpreted as an "n" and "a" in "Benicar", respectively. Also, "Benicar" and *Mevacor* are both available in a tablet dosage form and have overlapping strengths. Both products have 20-mg, and 40-mg tablets. The usual adult dosage for "Benicar" is 20 mg once a day while *Mevacor* can also be given 20 mg once a day. Cholesterol lowering and anti-hypertensive agents can be given in the same patient population. However, the sound of the "B" in "Benicar" and the "M" in *Mevacor* may distinguish the two tradenames from each other.

Even though there are existing tradenames that look and sound similar to "Benicar", there are distinguishing factors among those existing tradenames and "Benicar". OPDRA has no objection to the use of the proprietary name, "Benicar".

D. **(Confidential and proprietary.**

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secret and/or

confidential

commercial

information

## III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A. CONTAINER LABEL (5 mg, — mg, 20 mg, and 40 mg)

*30 count and 90 count bottles*

1. The drug product strengths on the principle panel should be differentiated among the products (ie. Different color, highlighted) to avoid confusion among the strengths.
2. The established name should be revised to state: Olmesartan medoxomil tablets.
3. The word "Tablets" should be taken out of the proprietary name in the principle panel.
4. The statement "Rx only" on the right side panel should be moved to the principle panel.
5. The statement "Dosage and use: See Package Insert" should be revised to state "Usual dosage: See Package Insert" as per 21 CFR 201.55.
6. The Sankyo logo on the principle panel is not shown. If the logo is shown, it should be no larger than 1/3 of the label and should not obscure any information on the principle panel.

B. CARTON LABELING (— mg, 20 mg, and 40 mg)

*Hospital Unit Dose Carton and Physician Sample Carton*

1. See appropriate comments above.
2. The blister packages were not submitted with the consult. Please submit blister packages for OPDRA review.

C. PACKAGE INSERT

1. The package insert only lists 20 mg and 40 mg tablets as the available strengths. However, the labels and labeling submitted by the sponsor consisted of 5 mg, —mg, 20 mg, and 40 mg strengths. According to the Division of Cardio-Renal Drug Products, the sponsor agreed with the Agency to supply a 5-mg strength for special populations. The package insert should reflect the additional 5-mg strength.

## IV. RECOMMENDATIONS:

OPDRA has no objection to the use of the proprietary name, "Benicar".

OPDRA recommends the above labeling revisions to encourage the safest possible use of the product.

OPDRA 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 Jennifer Fan at 301-827-3243.

/S/

Jennifer Fan, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur: /S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

/s/
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