CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-006

Name:	Chlorhexidine Gluconate Oral Rinse USP, 0.12%
Sponsor:	Morton Grove Pharmaceuticals, Inc.
Approval Date:	March 3, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-006

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Reviews / Information Included in this Review	
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Statistical Review(s)	
Microbiology Review(s)	
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Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-006

APPROVAL LETTER

ANDA 75-006

MAR 3 2004

Morton Grove Pharmaceuticals, Inc.
Attention: Sheeja T. George
6451 West Main Street
Morton Grove, IL 60053

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 15, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Chlorhexidine Gluconate Oral Rinse USP, 0.12%.

Reference is also made to your amendments dated January 22, August 1, and December 11, 2003, and February 10, 2004.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Chlorhexidine Gluconate Oral Rinse USP, 0.12%, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Peridex® Oral Rinse of Zila Pharmaceuticals, Inc.).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 3/3/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-006
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-600/N.Nashed/ 3/1/04
HFD-623/J.Fan/ 2/27/04
HFD-617/T.Vu/ 3/1/04
HFD-613/~~L.Golson~~/B. Weltzman 3/1/2004
HFD-613/J.Grace/ 3/1/2004

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F/T by

APPROVAL

Robert West
3/3/2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-006

APPROVED LABELING

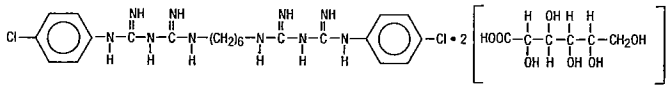
CHLORHEXIDINE GLUCONATE ORAL RINSE 0.12%

APPROVAL

MAR 03 2004

DESCRIPTION

Chlorhexidine gluconate oral rinse is an oral rinse containing 0.12% chlorhexidine gluconate (1,1'-hexamethylene bis [5-(p-chlorophenyl) biguanide] di-D-gluconate) in a base containing water, 11.6% alcohol, glycerin, PEG-40 sorbitan diisostearate, peppermint stick flavor, sodium saccharin, and FD&C Blue No. 1. Chlorhexidine gluconate oral rinse is a near-neutral solution (pH range 5-7). Chlorhexidine gluconate is a salt of chlorhexidine and gluconic acid. Its molecular formula is $C_{22}H_{30}Cl_2N_{10}\bullet 2C_6H_{12}O_7$, the molecular weight is 897.77 and it has the following structural formula:



CLINICAL PHARMACOLOGY

Chlorhexidine gluconate oral rinse provides microbicidal activity during oral rinsing. The clinical significance of chlorhexidine gluconate oral rinse's anti-microbial activities is not clear. Microbiological sampling of plaque has shown a general reduction of counts of certain assayed bacteria, both aerobic and anaerobic, ranging from 54-97% through six months' use.

Use of chlorhexidine gluconate oral rinse in a six-month clinical study did not result in any significant changes in bacterial resistance, overgrowth of potentially opportunistic organisms or other adverse changes in the oral microbial ecosystem. Three months after chlorhexidine gluconate use was discontinued, the number of bacteria in plaque had returned to baseline levels and resistance of plaque bacteria to chlorhexidine gluconate was equal to that at baseline.

Pharmacokinetics

Pharmacokinetic studies with a 0.12% chlorhexidine gluconate oral rinse indicate approximately 30% of the active ingredient, chlorhexidine gluconate, is retained in the oral cavity following rinsing. This retained drug is slowly released into the oral fluids. Studies conducted on human subjects and animals demonstrate chlorhexidine gluconate is poorly absorbed from the gastrointestinal tract. The mean plasma level of chlorhexidine gluconate reached a peak of 0.206 μg/g in humans 30 minutes after they ingested a 300 mg dose of the drug. Detectable levels of chlorhexidine gluconate were not present in the plasma of these subjects 12 hours after the compound was administered. Excretion of chlorhexidine gluconate occurred primarily through the feces (~90%). Less than 1% of the chlorhexidine gluconate ingested by these subjects was excreted in the urine.

INDICATIONS AND USAGE

Chlorhexidine gluconate oral rinse is indicated for use between dental visits as part of a professional program for the treatment of gingivitis as characterized by redness and swelling of the gingivae, including gingival bleeding upon probing. Chlorhexidine gluconate oral rinse has not been tested among patients with acute necrotizing ulcerative gingivitis (ANUG). For patients having coexisting gingivitis and periodontitis, see **PRECAUTIONS**.

CONTRAINDICATIONS

Chlorhexidine gluconate oral rinse should not be used by persons who are known to be hypersensitive to chlorhexidine gluconate.

WARNINGS

The effect of chlorhexidine gluconate oral rinse on periodontitis has not been determined. An increase in supragingival calculus was noted in clinical testing in chlorhexidine gluconate oral rinse users compared with control users. It is not known if chlorhexidine gluconate use results in an increase in subgingival calculus. Calculus deposits should be removed by a dental prophylaxis at intervals not greater than six months. Hypersensitivity and generalized allergic reactions have occurred. See **CONTRAINDICATIONS.**

PRECAUTIONS

General

1. For patients having coexisting gingivitis and periodontitis, the presence or absence of gingival inflammation following treatment with chlorhexidine gluconate oral rinse should not be used as a major indicator of underlying periodontitis.
2. Chlorhexidine gluconate oral rinse can cause staining of oral surfaces, such as tooth surfaces, restorations, and the dorsum of the tongue. Not all patients will experience a visually significant increase in toothstaining. In clinical testing, 56% of chlorhexidine gluconate oral rinse users exhibited a measurable increase in facial anterior stain, compared to 35% of control users after six months; 15% of chlorhexidine gluconate oral rinse users developed what was judged to be heavy stain, compared to 1% of control users after six months. Stain will be more pronounced in patients who have heavier accumulations of unremoved plaque.

   Stain resulting from use of chlorhexidine gluconate oral rinse does not adversely affect health of the gingivae or other oral tissues. Stain can be removed from most tooth surfaces by conventional professional prophylactic techniques. Additional time may be required to complete the prophylaxis.

   Discretion should be used when prescribing to patients with anterior facial restorations with rough surfaces or margins. If natural stain cannot be removed from these surfaces by a dental prophylaxis, patients should be excluded from chlorhexidine gluconate treatment if permanent discoloration is unacceptable. Stain in these areas may be difficult to remove by dental prophylaxis and on rare occasions may necessitate replacement of these restorations.
3. Some patients may experience an alteration in taste perception while undergoing treatment with chlorhexidine gluconate oral rinse. Rare instances of permanent taste alteration following chlorhexidine gluconate oral rinse use have been reported.

Pregnancy: Teratogenic Effects - Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at chlorhexidine gluconate doses up to 300 mg/kg/day and 40 mg/kg/day, respectively, and have not revealed evidence of harm to the fetus. However, adequate and well-controlled studies in pregnant women have not been done. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when chlorhexidine gluconate is administered to a nursing woman.

In parturition and lactation studies with rats, no evidence of impaired parturition or of toxic effects to suckling pups was observed when chlorhexidine gluconate was administered to dams at doses up to 100 mg/kg/day.

Pediatric Use

Clinical effectiveness and safety of chlorhexidine gluconate oral rinse have not been established in pediatric patients under the age of 18.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a drinking water study in rats, carcinogenic effects were not observed in two mammalian *in vivo* mutagenesis studies with chlorhexidine gluconate. The highest

doses of chlorhexidine used in a mouse dominant-lethal assay and a hamster cytogenetics test were 1000 mg/kg/day and 250 mg/kg/day, respectively. No evidence of impaired fertility was observed in rats at doses up to 100 mg/kg/day.

ADVERSE REACTIONS

The most common side effects associated with chlorhexidine gluconate oral rinses are (1) an increase in staining of teeth and other oral surfaces, (2) an increase in calculus formation, and (3) an alteration in taste perception; see **WARNINGS** and **PRECAUTIONS**. Oral irritation and local allergy-type symptoms have been spontaneously reported as side effects associated with use of chlorhexidine gluconate rinse. The following oral mucosal side effects were reported during placebo-controlled adult clinical trials: aphthous ulcer, grossly obvious gingivitis, trauma, ulceration, erythema, desquamation, coated tongue, keratinization, geographic tongue, mucocele, and short frenum. Each occurred at a frequency of less than 1%.

Among postmarketing reports, the most frequently reported oral mucosal symptoms associated with chlorhexidine gluconate oral rinse are stomatitis, gingivitis, glossitis, ulcer, dry mouth, hypesthesia, glossal edema, and paresthesia.

Minor irritation and superficial desquamation of the oral mucosa have been noted in patients using chlorhexidine gluconate oral rinse.

There have been cases of parotid gland swelling and inflammation of the salivary glands (sialadenitis) reported in patients using chlorhexidine gluconate oral rinse.

OVERDOSAGE

Ingestion of 1 or 2 ounces of chlorhexidine gluconate oral rinse by a small child (~10 kg body weight) might result in gastric distress, including nausea, or signs of alcohol intoxication. Medical attention should be sought if more than 4 ounces of chlorhexidine gluconate oral rinse is ingested by a small child or if signs of alcohol intoxication develop.

DOSAGE AND ADMINISTRATION

Chlorhexidine gluconate oral rinse therapy should be initiated directly following a dental prophylaxis. Patients using chlorhexidine gluconate oral rinse should be reevaluated and given a thorough prophylaxis at intervals no longer than six months.

Recommended use is twice daily oral rinsing for 30 seconds, morning and evening after toothbrushing. Usual dosage is 1/2 fl oz (marked in cup) of undiluted product. Patients should be instructed to not rinse with water, or other mouthwashes, brush teeth, or eat immediately after using chlorhexidine gluconate oral rinse. Chlorhexidine gluconate oral rinse is not intended for ingestion and should be expectorated after rinsing.

HOW SUPPLIED

Chlorhexidine Gluconate Oral Rinse is supplied as a light blue liquid in 1 pint (473 mL) child-resistant bottles, individually cartoned with a dosage cup.

Store above freezing (32 °F or 0 °C).

Dispense in original container or in amber glass bottles.

Rx Only

Product No.: 8154

Manufactured By:
Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

28154
ISS. 1-99

Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

D5-006

CHLORHEXIDINE GLUCONATE ORAL RINSE 0.12%

1 PINT (473 mL) FINAL PRINTED LABEL

MGP

NDC 60432-154-16

CHLORHEXIDINE GLUCONATE ORAL RINSE 0.12%

DIRECTIONS FOR USE: Fill dosage cup to the ½ fl oz line. Swish in mouth undiluted for 30 seconds then spit. Use after breakfast and before bedtime. Or, use as prescribed.

NOTE: To minimize medicinal taste, do not rinse with water immediately after use.

INGREDIENTS: 0.12% chlorhexidine gluconate in a base containing water, 11.6% alcohol, glycerin, USP, PEG-40 sorbitan diisostearate, peppermint stick flavor, sodium saccharin, USP, and FD&C Blue No. 1.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Store above freezing (32 °F or 0 °C).

Rx Only

NET: 1 Pint (473 mL)

WHAT TO EXPECT WHEN USING CHLORHEXIDINE GLUCONATE ORAL RINSE

Your dentist has prescribed chlorhexidine gluconate oral rinse to treat your gingivitis–to help reduce the redness and swelling of your gums, and also to help you control any gum bleeding. Use chlorhexidine gluconate oral rinse regularly, as directed by your dentist, in addition to daily brushing and flossing. Spit out after use, chlorhexidine gluconate oral rinse should not be swallowed.

Chlorhexidine gluconate oral rinse may cause some tooth discoloration, or increases in tartar (calculus) formation, particularly in areas where stain and tartar usually form. It is important to see your dentist for removal of any stain or tartar at least every six months, or more frequently if your dentist advises.

- Both stain and tartar can be removed by your dentist or hygienist. Chlorhexidine gluconate oral rinse may cause permanent discoloration of some front-tooth fillings.
- To minimize discoloration, you should brush and floss daily, emphasizing areas which begin to discolor.
- Local hypersensitivity and sometimes generalized allergic reactions have also been reported. Chlorhexidine gluconate oral rinse should not be used by persons who have a sensitivity to it or its components.

Chlorhexidine gluconate oral rinse may taste bitter to some patients and can affect how foods and beverages taste. This will become less noticeable in most cases with continued use of chlorhexidine gluconate oral rinse.

- To avoid taste interference, rinse with chlorhexidine gluconate oral rinse *after* meals. Do not rinse with water or other mouthwashes immediately after rinsing with chlorhexidine gluconate oral rinse.

If you have any questions or comments about chlorhexidine gluconate oral rinse, contact your dentist or pharmacist.

See accompanying package insert for prescribing information.

APPROVED MAR 03 2004

PLACE PHARMACY LABEL HERE

Dispense in original container or in amber glass.

Manufactured By:
Morton Grove Pharmaceuticals, Inc. 50-8154-16
Morton Grove, IL 60053 ISS. 6-98

N 3 60432-154-16 1

DIRECTIONS FOR USE:
Fill dosage cup to the ½ fl oz line. Swish in mouth undiluted for 30 seconds then spit. Use after breakfast and before bedtime. Or, use as prescribed.

NOTE: To minimize medicinal taste, do not rinse with water immediately after use.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured By:
Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

MGP

NDC 60432-154-16

CHLORHEXIDINE GLUCONATE ORAL RINSE 0.12%

APPROVAL

MAR 03 2004

Rx Only

NET: 1 Pint (473 mL)

CHLORHEXIDINE GLUCONATE ORAL RINSE

NDC 60432-154-16

INGREDIENTS: 0.12% chlorhexidine gluconate in a base containing water, 11.6% alcohol, glycerin, USP, PEG-40 sorbitan diisostearate, peppermint stick flavor, sodium saccharin, USP, and FD&C Blue No. 1.

See accompanying package insert for prescribing information.

Store above freezing (32 °F or 0 °C).

Dispense in original container or in amber glass.

See top flap of carton for lot number and expiration date.

Manufactured By:
Morton Grove
Pharmaceuticals, Inc.
Morton Grove, IL 60053

5-50-8154-16
ISS. 6-98

WHAT TO EXPECT WHEN USING CHLORHEXIDINE GLUCONATE ORAL RINSE

Your dentist has prescribed chlorhexidine gluconate oral rinse to treat your gingivitis–to help reduce the redness and swelling of your gums, and also to help you control any gum bleeding. Use chlorhexidine gluconate oral rinse regularly, as directed by your dentist, in addition to daily brushing and flossing. Spit out after use, chlorhexidine gluconate oral rinse should not be swallowed.

Chlorhexidine gluconate oral rinse may cause some tooth discoloration, or increases in tartar (calculus) formation, particularly in areas where stain and tartar usually form. It is important to see your dentist for removal of any stain or tartar at least every six months, or more frequently if your dentist advises.

- Both stain and tartar can be removed by your dentist or hygienist. Chlorhexidine gluconate oral rinse may cause permanent discoloration of some front-tooth fillings.
- To minimize discoloration, you should brush and floss daily, emphasizing areas which begin to discolor.
- Local hypersensitivity and sometimes generalized allergic reactions have also been reported. Chlorhexidine gluconate oral rinse should not be used by persons who have a sensitivity to it or its components.

Chlorhexidine gluconate oral rinse may taste bitter to some patients and can affect how foods and beverages taste. This will become less noticeable in most cases with continued use of chlorhexidine gluconate oral rinse.

- To avoid taste interference, rinse with chlorhexidine gluconate oral rinse *after* meals. Do not rinse with water or other mouthwashes immediately after rinsing with chlorhexidine gluconate oral rinse.

If you have any questions or comments about chlorhexidine gluconate oral rinse, contact your dentist or pharmacist.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-006

LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-006** Date of Submission: **November 12, 1997**

Applicant's Name: **Morton Grove Pharmaceuticals, Inc.**

Established Name: **Chlorhexidine Gluconate Oral Rinse**

Labeling Deficiencies:

1. CONTAINER (473 mL)

   a. Revise the DIRECTIONS FOR USE to read as follows:

      ...30 seconds then spit. Use after breakfast and before bedtime. Or...

   b. WHAT TO EXPECT WHEN USING CHLORHEXIDINE GLUCONATE ORAL RINSE

      i. Insert the following text as the last sentence of paragraph one:

         Spit out after use, chlorhexidine gluconate oral rinse should not be swallowed.

      ii. Revise paragraph two to read as follows:

         ...particularly in areas where stain and tartar usually form. It is important to see...

      iii. Revise the third bullet to read as follows:

         - Local hypersensitivity and sometimes generalized allergic...

      iv. Paragraph three - Delete the last sentence of this paragraph. [———————————...]

      v. Revise the fourth bullet to read as follows:

         - To avoid...water or other mouthwashes immediately after rinsing with chlorhexidine gluconate oral rinse.

c. We note the innovator has designated an area on the container label for the placement of the pharmacy label. You have not indicated that an area is reserved for this on your label. Please comment and/or revise.

2. CARTON (1 x 472 mL)

See comments a and b under CONTAINER.

3. INSERT

a. DESCRIPTION

Delete —— from the listing of inactive ingredients in 2 places.

b. CLINICAL PHARMACOLOGY

i. Paragraph one - Delete " ———— " from the last sentence of paragraph two.

ii. Pharmacokinetics

A). Revise the first sentence to read as follows:

...with a 0.12% chlorhexidine gluconate oral rinse indicate...active ingredient.

B). Delete the "hyphen" that appears between "300" and "mg".

c. WARNINGS

Revise to read as follows:

...It is not known if chlorhexidine gluconate use results in an...six months. Hypersensitivity and generalized allergic reactions have occurred. See CONTRAINDICATIONS.

d. PRECAUTIONS

i. General

A). Number 2, second paragraph - Stain resulting from use of...excluded from chlorhexidine gluconate treatment if permanent...Stain in these areas...

B). Number 3 - ...with chlorhexidine gluconate oral rinse. Rare instances of...rinse use have...

ii. Usage in Pregnancy - Revise this subsection heading to read "Pregnancy: Teratogenic Effects - Pregnancy Category B". In addition, revise the subsection to read as follows:

Reproduction studies have been performed in rats and rabbits at chlorhexidine gluconate doses up to 300 mg/day and 40 mg/kg/day, respectively, and have not revealed evidence of harm to the fetus. However, adequate and well-controlled studies in pregnant women have not been done. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

iii. Nursing Mothers - Revise to read as follows:

...exercised when chlorhexidine gluconate is administered...

In parturition...chlorhexidine gluconate was administered to dams at doses up to 100 mg/kg/day.

iv. Carcinogenesis, Mutagenesis - Revise this subsection heading to read "Carcinogenesis, Mutagenesis, Impairment of Fertility". In addition, revise the subsection to read as follows:

In a drinking water study in rats, carcinogenic effects were not observed in two mammalian *in vivo* mutagenesis studies with chlorhexidine gluconate. The highest doses of chlorhexidine used in a mouse dominant-lethal assay and a hamster cytogenetics test were 1000 mg/kg/day and 250 mg/kg/day, respectively. No evidence of impaired fertility was observed in rats at doses up to 100 mg/kg/day.

e. ADVERSE REACTIONS

i. Paragraph one, number 3 - Revise to read as follows:

...PRECAUTIONS. Oral irritation and local allergy-type symptoms have been spontaneously reported as side effects associated with use of chlorhexidine gluconate rinse. The following oral mucosal side effects were reported during placebo-controlled adult clinical trials: aphthous ulcer, grossly obvious gingivitis, trauma, ulceration, erythema, desquamation, coated tongue, keratinization, geographic tongue, mucocele, and short frenum. Each occurred at a frequency of less than 1%.

ii. Insert the following text to appear as the second paragraph:

Among postmarketing reports, the most frequently reported oral mucosal symptoms associated with chlorhexidine gluconate oral rinse are stomatitis, gingivitis, glossitis, ulcer, dry mouth, hypesthesia, glossal edema, and paresthesia.

iii. Revise paragraph two to read as follows:

Minor irritation...using chlorhexidine gluconate oral rinse.

iv. Revise the last paragraph to read as follows:

There have been cases of parotid gland swelling and inflammation of the salivary glands (sialadenitis) reported in patients using chlorhexidine gluconate oral rinse.

f. DOSAGE AND ADMINISTRATION

Chlorhexidine gluconate oral rinse therapy should be initiated...

Please revise your container labels, carton and insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

John D. Bruce for/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No

Container Labels:

Carton Labeling:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Peridex Oral Rinse

NDA Number: 19-028

NDA Drug Name: Peridex Oral Rinse

NDA Firm: Procter and Gamble Company

Date of Approval of NDA Insert and supplement #: January 8, 1997/S-009
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Approved container labels in file folder.
Basis of Approval for the Carton Labeling: Approved carton labeling in file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

******NOTES/QUESTIONS TO THE CHEMIST:******

1. **Does the dosage cup provided deliver the labeled amount? I couldn't find any data on the cup at all. I wanted to be assured the cup will be packaged with the bottle and if it is clearly market ½ oz.**

FOR THE RECORD:

1. Review based on the labeling of the listed drug(Peridex Oral Rinse; 19-028/S-009; Approved January 8, 1997, Revised December 1996).

2. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

   NDA: Store above freezing (32°F or 0°C). Dispense in bottle as provided or in amber glass.

   ANDA: Store above freezing (32°F or 0°C). Dispense in original container or in amber glass bottles.

   USP: Not a monograph in the USP of PF.

4. Product Line:

   The innovator markets their product in bottles containing 473 mL in cartons of 3.

   The applicant proposes to market their product in bottles containing 473 mL in cartons of 1.

5. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 60 and 61, Vol. 2.1.

6. All manufacturing will be performed by Morton Grove Pharmaceuticals, Inc.. All outside firms are utilized for testing. See pages 202 and 593, Vol. 2.1.

7. Container/Closure:

   This product will be packaged in 16 oz **Amber** Round Bottle with a CRC closure.

8. The firm originally submitted this application in January with a different formulation. A refuse to file letter was sent because this product was classified as a topical and therefore had to have the same ingredients.

Date of Review: December 3, 1997

Date of Submission: November 12, 1997

Reviewer: Carol A. Holquist **Date:** 2/10/98

Team Leader: John Grace **Date:** 2/11/98

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cc:

ANDA 75-006
DUP/DIVISION FILE
HFD-613/CHolquist/JGrace (no cc)
12/3/97/X:\NEW\FIRMSAM\MORTON\LTRS&REV\75006NA1.L
Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-006 Date of Submission: July 10, 1998

Applicant's Name: Morton Grove Pharmaceuticals, Inc.

Established Name: Chlorhexidine Gluconate Oral Rinse, 0.12%

Labeling Deficiencies:

1. CONTAINER (473 mL)

   Satisfactory

2. CARTON (1 x 473 mL)

   Satisfactory

3. INSERT

   a. PRECAUTIONS

      i. General

         A) Revise to delete the second sentence, "[redacted]..." from Number 3.

         B) Revise the ultimate sentence of Number 3 to read, ...alteration following chlorhexidine...

      ii. Pregnancy

         Revise the first sentence to read, "...300 mg/kg/day..." (add "kg")

   b. DOSAGE AND ADMINISTRATION

      Revise so that the following becomes the third sentence of the second paragraph:

      Patients should be instructed to not rinse with water, or other mouthwashes, brush teeth, or eat immediately after using chlorhexidine gluconate oral rinse.

Please revise your package insert labeling, as instructed above, and submit in final print.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

John D. Grace for

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No

Container Labels: (473 mL)
Satisfactory as of July 10, 1998, submission

Carton Labeling: (1 x 473 mL)
Satisfactory as of July 10, 1998, submission

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Peridex Oral Rinse

NDA Number: 19-028

NDA Drug Name: Peridex Oral Rinse

NDA Firm: Procter and Gamble Company

Date of Approval of NDA Insert and supplement #: January 8, 1997/S-009
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Approved container labels in file folder.
Basis of Approval for the Carton Labeling: Approved carton labeling in file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

******NOTES/QUESTIONS TO THE CHEMIST:******

1. **Does the dosage cup provided deliver the labeled amount? I couldn't find any data on the cup at all. I wanted to be assured the cup will be packaged with the bottle and if it is clearly market ½ oz.**

FOR THE RECORD:

1. Review based on the labeling of the listed drug(Peridex Oral Rinse; 19-028/S-009; Approved January 8, 1997, Revised December 1996).

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7. Container/Closure:

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8. The firm originally submitted this application in January with a different formulation. A refuse to file letter was sent because this product was classified as a topical and therefore had to have the same ingredients.

Date of Review:
December 10, 1998

Date of Submission:
July 10, 1998

Primary Reviewer:

Date:
12/10/98

Team Leader:

Date:
12/10/98

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cc:

ANDA: 75-006
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
ldg/12/10/98/X:\NEW\FIRMSAM\MORTON\LTRS&REV\75006NA2.L
Review

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-006 Date of Submission: February 9, 1999 and July 10, 1998 (Amendments)

Applicant's Name: Morton Grove Pharmaceuticals, Inc.

Established Name: Chlorhexidine Gluconate Oral Rinse, 0.12%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (473 mL)
Satisfactory as of July 10, 1998, submission

Carton Labeling: (1 x 473 mL)
Satisfactory as of July 10, 1998, submission

Professional Package Insert Labeling:
Satisfactory as of February 9, 1999, submission

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Peridex Oral Rinse

NDA Number: 19-028

NDA Drug Name: Chlorhexidine Gluconate Oral Rinse

NDA Firm: Procter & Gamble Company

Date of Approval of NDA Insert and supplements #007, 008, 009: January 8, 1997

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No